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Optimal solution for a cancer radiotherapy problem with a maximal damage constraint on normal tissues

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Abstract

In Bertuzzi et al. [1] we addressed the problem of finding the optimal radiotherapy fractionation scheme, representing the response to radiation of tumour and normal tissues by the LQ model including exponential repopulation and sublethal damage due to incomplete repair. We formulated the nonlinear programming problem of maximizing the overall tumour damage, while keeping the damages to the late and early responding normal tissues within a given admissible level. In the present paper we show the results for a simpler optimization problem, containing only the constraint related to the late normal tissue that reduces to an equality constraint under suitable assumptions. In fact, it has been shown in [1] that, suitably choosing the maximal damage values, the problem here considered is equivalent to the more general one, in that their extremals, and then their optimal solutions, coincide. The optimum is searched over a single week of treatment and its possible structures are identified. We characterize the optimal solution in terms of model parameters. Apart from limit values of the parameters, we prove that the optimal solution is unique and never consisting of five equal fractions per week. This is interesting in comparison to the uniform fractionation schemes commonly used in radiotherapy.

Keywords: Nonlinear programming; Cancer radiotherapy; Linear-quadratic model.

1 Introduction

Among the methods that aim to improve the outcome of cancer radiotherapy treatment, the optimization of the protocol has a main role (see, for instance, [2, 3]). The protocol optimization methods are based on models of the radiation response of the tumour and the normal tissues. The processes that characterize this response are denoted as the "four Rs" of radiotherapy: repair of the radiation damage, redistribution of cells among the cell-cycle phases, repopulation due to the regrowth of the cells surviving the irradiation, reoxygenation of tissues [4].

The so-called linear-quadratic (LQ) model of the radiation effect [5, 6, 2] appears to be the most regularly used model to represent the relation between a single radiation dose d (Gy) and the fraction S of cells surviving the irradiation

$$S = \exp(-\alpha d - \beta d^2)\,,$$

where the radiosensitivity parameters, α and β, account for non-repairable lesions to DNA and, respectively, for the lethal misrepair events occurring in the repair process of DNA double strand breaks [7]. When multiple doses are delivered and the cell repopulation is taken into account, the survival fraction is expressed by more complex expressions compared with the basic formulation given above, as it will be seen in Section 2 [8, 9].

A resensitization term, which was intended to account for both the redistribution and the reoxygenation, has been included in the LQ model leading to the LQR model, proposed by Brenner at al. [10]. The LQR model was applied to a variety of in vitro and in vivo cell populations and its parameters were estimated from the data [10]. However, the assessment of these parameters may be critical in highly heterogeneous populations such as human tumours. Different approaches to represent the kinetic effects of repopulation and reoxygenation have been followed in studies where the geometry of the tumour mass was explicitly taken into account [11, 12]. The diffusion/consumption of oxygen in the tumour cell aggregate and the hypoxia-induced cell death have been represented in models of the radiation response of tumour cords [13] and of multicellular tumour spheroids [14]. Simulation models with a cell-cycle structure were also proposed to account for the different phase-specific radiosensitivities of the cells [15, 16]. A recent review by O'Rourke et al. [17] examines the LQ formalism with emphasis on the modelling of repopulation and redistribution mechanisms.

The LQ and the LQR models have been used in recent papers looking for an optimal radiotherapeutic strategy, consisting in achieving the best trade-off between maximizing the tumour cell kill and sparing the normal tissues. For instance, Fowler [18, 9] used the LQ model with repopulation term to investigate optimum schedules for head and neck cancer, taking into account both the early reacting normal tissues and the late complications. In these papers, the Author proposed an empirical procedure in order to optimize the treatment overall time, keeping fixed the late tissue damage and using schedules with uniform fraction size. Optimum overall times were found to be in the range 22-32 days for a treatment with one fraction/day five times a week. Yang and Xing [19], using the complete LQR model with parameter values taken from the literature, investigated by a numerical procedure (simulated annealing) the optimum radiotherapy schemes for fast proliferating and slowly proliferating tumours. The optimization procedure searched for the highest tumour biologically effective dose (BED $= -\ln(S)/\alpha$) over the total treatment length while the BED of the late normal tissue was kept constant. Interestingly, the resulting optimal fractionation scheme was not necessarily uniform.

In the present report, as in the paper [1], we propose the analytical formulation of an optimal radiotherapy problem. In Section 2, we describe the cell response to radiation by the LQ model, including the sublethal damage due to incomplete repair and the repopulation term. The aim is to find the size of the five weekly fractions maximizing the overall tumour damage, while keeping the damages to normal tissues within a given admissible level. In general both the early and the late normal tissue constraints are included when an optimal radiotherapy problem is formulated. However, here we report a detailed study of a simpler problem including only the constraint on the late responding tissue, which is of interest since in many practical cases the late constraint prevails, as shown in [1]. In Section 3, after guaranteeing the existence of an optimal solution, we give the possible structures of the solution, using the classical nonlinear programming necessary conditions. In Section 4, we show that the optimal solution is a function of a global parameter Q that depends on both tumour and late normal tissue. In particular, we find four intervals of Q values in which the solution structure is invariant. Except the limit value $Q = 0$, we prove the uniqueness of the optimal solution and characterize the optimal doses in terms of model parameters.

A remarkable result emerging from the present study is that the tumour α/β ratio strongly affects the fractionation scheme, that is, hypofractionation is convenient for small α/β ratios whereas the optimal fractionation tends to be uniform for large α/β. This result formalizes in mathematical terms previous observations [20, 21]. In particular for tumours with small α/β, the use of large doses in hypofractionated treatments may become acceptable in view of recent technological advances that allow to spatially modulate the radiation intensity.

2 Formulation of an optimal radiotherapy problem with a maximal damage constraint on normal tissues.

The response to radiation of a (homogeneous) cell population is described in the present paper by the LQ model, including the lethal and sublethal damages and the cell repopulation [10, 19, 9, 17]. We assume that the radiation treatment is given over an integer number of weeks, ν, and that one fraction per day is delivered, leaving a treatment break at each weekend according to the usual medical practice. Denoting by $d_i \geq 0, \quad i = 1, 2, \dots, 5\nu$, the radiation dose given at day i-th, the cumulated effect due to the instantaneous lethal damage is

$$E_1 = \alpha \sum_{i=1}^{5\nu} d_i + \beta \sum_{i=1}^{5\nu} d_i^2 \,, \tag{2.1}$$

where α and β are the (strictly positive) LQ constants characterizing the intrinsic radiosensitivity of the population. The sublethal damage due to binary misrepair is modelled as:

$$E_2 = 2\beta \sum_{i=2}^{5\nu} d_i \left(\sum_{j=1}^{i-1} d_j \mathrm{e}^{-(i-j)\gamma} \right) , \tag{2.2}$$

where γ is the ratio between the inter-fraction time interval Δ (one day) and the misrepair time constant τ_R. Finally the cell repopulation is represented by:

$$E_3 = \begin{cases} \dfrac{\ln(2)[T - T_k]}{T_P} , & T \geq T_k \, , \\ \\ 0 \ \text{ elsewhere} \, , \end{cases} \tag{2.3}$$

where the overall treatment time is $T = 7\nu - 3$ days (number of days between the 1st and the last dose), T_P is the repopulation doubling time and T_k is the starting time of compensatory proliferation (kick-off time). Therefore the fraction of surviving cells is given by:

$$S = \exp(-E_1 - E_2 + E_3) \, .$$

The above model of the response to radiation is used to describe both tumour and normal tissues. In this context, for the normal tissue we distinguish the early and the late response. In the following, the parameters in equations (2.1) - (2.3) related to the early and late response are indexed by subscripts “e” and “l” respectively.

Since the values reported in the literature for the misrepair time constants are always less than 4.0 h ($\tau_R \approx 0.5$ h, $\tau_{Re} \approx 0.5$ h, $\tau_{Rl} \approx 4.0$ h) and $\Delta = 24$ h, γ, γ_e, γ_l are larger than 6.0 [19]. This allows to simplify the expression of E_2 for the three tissues considered as follows:

$$\tilde{E}_2 = 2\beta \mathrm{e}^{-\gamma} \sum_{i=2}^{5\nu} d_{i-1} d_i \, . \tag{2.4}$$

In this paper we formulate an optimal radiotherapy problem, assuming that ν, and then the overall treatment time (T), is fixed. We aim at minimizing the fraction of tumour surviving cells S (and in particular its logarithm) with respect to the radiation doses:

$$\ln(S) = -E_1 - \tilde{E}_2 + E_3 \, .$$

Noting that E_3 does not depend on the radiation doses, this is equivalent to minimize only $-E_1 - \tilde{E}_2$. At the same time we have to account for suitable constraints related to the maximal admissible damage to the normal tissue. Denoting by C_e and C_l the log of the maximal damage to the early and the late responding tissue respectively, the constraints take the form:

$$-\ln(S_e) = E_{1e} + \tilde{E}_{2e} - E_{3e} \leq C_e \, , \tag{2.5}$$

$$-\ln(S_l) = E_{1l} + \tilde{E}_{2l} \leq C_l \,. \tag{2.6}$$

where the constraint (2.6) does not contain the cell repopulation term, since it is negligible for the late responding tissue.

To simplify the optimization problem (that is to reduce the number of variables) and at the same time to strengthen the constraints (2.5) and (2.6) we equally distribute the damage over the weeks and then we formulate the optimization problem over a single week, assuming that the obtained solution is repeated for each week of the treatment.

As well known [22, 23, 24], to reduce the damage to normal tissues, the radiation intensity is spatially modulated by suitable technological devices. Therefore we introduce a coefficient $f \in (0, 1)$, that globally accounts for the attenuation of the doses received by the normal tissues. This means that with reference to equations (2.5) and (2.6) the actual doses acting on normal tissues are $f d_i, i = 1, \ldots, 5$.

Let us introduce the notations:

$$\rho = \frac{\alpha}{\beta}\,, \quad \rho_e = \frac{\alpha_e}{f\beta_e}\,, \quad \rho_l = \frac{\alpha_l}{f\beta_l}\,, \quad k_e = \frac{C_e + E_{3e}}{f^2\nu\beta_e}\,, \quad k_l = \frac{C_l}{f^2\nu\beta_l}\,. \tag{2.7}$$

We observe that typical values of the α/β ratio for early and late normal tissue reported in the literature [25] are always such that $\rho_e > \rho_l$. Defining the 5-dimensional vector d with components $d_i, i = 1, \ldots, 5$, the constraints (2.5) and (2.6) can be written in the form:

$$g_e(d) = \rho_e \sum_{i=1}^{5} d_i + \sum_{i=1}^{5} d_i^2 + 2\mathrm{e}^{-\gamma_e} \sum_{i=2}^{5} d_{i-1}d_i - k_e \leq 0\,, \tag{2.8}$$

$$g_l(d) = \rho_l \sum_{i=1}^{5} d_i + \sum_{i=1}^{5} d_i^2 + 2\mathrm{e}^{-\gamma_l} \sum_{i=2}^{5} d_{i-1}d_i - k_l \leq 0\,. \tag{2.9}$$

Although both the early and the late normal tissue constraints should be included when a general optimal radiotherapy problem is formulated, in the present paper we show in more details the results for a simpler optimization problem, containing only the late constraint $g_l(d)$, as to an equality constraint. Indeed, it has been shown in [1] that, under suitable assumptions for the maximal damage values k_e and k_l, the latter problem is equivalent to the general problem with constraints (2.8) and (2.9), in that their extremals, and then their optimal solutions, coincide (see Theorem 5.3 in [1]). We stress that considering the constraint $g_l(d) = 0$ is not restrictive as all the extremals of the problem with constraint $g_l(d) \leq 0$ belong to the boundary, see [1]).

Let us then consider the following optimization problem.

Problem 2.1 *Minimize the function:*

$$\tilde{J}(d) = -\rho \sum_{i=1}^{5} d_i - \sum_{i=1}^{5} d_i^2 - 2\mathrm{e}^{-\gamma} \sum_{i=2}^{5} d_{i-1}d_i\,, \tag{2.10}$$

on the admissible set:

$$D = \{d \in R^5 | \;\; g_l(d) = 0\,, \;\; g_i(d) = -d_i \leq 0\,, \; i = 1, \ldots, 5\}\,. \tag{2.11}$$

□

3 Existence and structure of the optimal solution.

In order to simplify the study of Problem 2.1, we substitute the equality constraint into the cost function, obtaining:

$$\tilde{J}(d) = 2\left(\mathrm{e}^{-\gamma_l} - \mathrm{e}^{-\gamma}\right)\left[\frac{\rho_l - \rho}{2\left(\mathrm{e}^{-\gamma_l} - \mathrm{e}^{-\gamma}\right)}\sum_{i=1}^{5} d_i + \sum_{i=2}^{5} d_{i-1}d_i - \frac{k_l}{2\left(\mathrm{e}^{-\gamma_l} - \mathrm{e}^{-\gamma}\right)}\right]\,.$$

Defining the global parameter

$$Q = \frac{\rho - \rho_l}{2\left(\mathrm{e}^{-\gamma_l} - \mathrm{e}^{-\gamma}\right)}\,, \tag{3.1}$$

and noting that $\gamma_l < \gamma$ [26, 19], the problem of minimizing $\tilde{J}(d)$ on D is equivalent to minimizing

$$J(d) = -Q\sum_{i=1}^{5} d_i + \sum_{i=2}^{5} d_{i-1}d_i$$

on D.

A first important observation is that Problem 2.1 surely admits some optimal solutions. Indeed the admissible set (2.11) is compact and the cost function (2.10) is continuous. Then the Weierstrass' theorem [27] guarantees the existence of optimal solutions. It is evident that Problem 2.1 is not convex and therefore we can only use the optimal necessary conditions given by the Fritz John Theorem [27].

The Lagrangian function associated to Problem 2.1 is:

$$L(d, \lambda_0, \eta_l, \eta) = \lambda_0 J(d) + \lambda g_l(d) - \sum_{i=1}^{5} \eta_i d_i\,,$$

where λ_0, λ are scalar multipliers and η (the 5-dimensional vector with components $\eta_i, i = 1, \ldots, 5$) is the multiplier vector related to the inequality constraints.

The necessary minimum and admissibility conditions are:

$$\frac{\partial L}{\partial d_1} = \lambda_0(-Q + d_2) + \lambda(2d_1 + \rho_l + 2e^{-\gamma_l} d_2) - \eta_1 = 0\,, \tag{3.2}$$

$$\frac{\partial L}{\partial d_i} = \lambda_0(-Q + d_{i-1} + d_{i+1}) + \lambda[2d_i + \rho_l + 2e^{-\gamma_l}(d_{i-1} + d_{i+1})] - \eta_i = 0\,, \quad i = 2, 3, 4\,, \tag{3.3}$$

$$\frac{\partial L}{\partial d_5} = \lambda_0(-Q + d_4) + \lambda(2d_5 + \rho_l + 2e^{-\gamma_l} d_4) - \eta_5 = 0\,, \tag{3.4}$$

$$\eta_i d_i = 0\,, \quad i = 1, \ldots, 5\,, \tag{3.5}$$

$$g_l(d) = 0\,, \tag{3.6}$$

$$d_i \geq 0\,, \quad i = 1, \ldots, 5\,, \tag{3.7}$$

$$\lambda_0, \eta_i \geq 0\,, \quad i = 1, \ldots, 5\,, \tag{3.8}$$

where λ_0, λ, η_i, $i = 1, \ldots, 5$, cannot be simultaneously equal to zero. It is easy to verify that it must be $\lambda_0 > 0$. In fact, with $\lambda_0 = 0$, there exists no λ verifying the above conditions: if $\lambda < 0$ it follows $\eta_i < 0$, $i = 1, \ldots, 5$; if $\lambda = 0$ all the multipliers are zero; if $\lambda > 0$ it is $\eta_i > 0$, $i = 1, \ldots, 5$ and then $d = 0$, which is not admissible as it cannot satisfy the constraint (3.6).

Therefore we assume $\lambda_0 = 1$. In order to find the possible structures of the solutions, we consider the multiplier λ fixed and we solve the system of equations (3.2) - (3.5) with respect to the variables d_i, $\eta_i, i = 1, \ldots, 5$. We define the following quantities δ, σ, τ:

$$\begin{aligned} \delta(\lambda) &= -Q + \lambda\rho_l\,, \\ \sigma(\lambda) &= 2\lambda\,, \\ \tau(\lambda) &= 1 + 2\lambda e^{-\gamma_l}\,. \end{aligned} \tag{3.9}$$

and we prove a first result.

Theorem 3.1 *There are $2^5 - 1$ possible structures for the solutions d of Problem 2.1. The solutions may be grouped into 10 mutually exclusive classes, as reported in Table 1. The classes are characterized by the number of non-zero doses, as well as by the number of consecutive non-zero doses. The possible structures of each class are equivalent, in that they have the same values of the non-zero doses and then give the same value of the cost function J.*

Class	Equivalent structures		
	Representative	Number	Elements
$d^{(1)}$	$(A^{(1)}\ 0\ 0\ 0\ 0)$	5	$(A^{(1)}\ 0\ 0\ 0\ 0)$, $(0\ A^{(1)}\ 0\ 0\ 0)$, $(0\ 0\ A^{(1)}\ 0\ 0)$, $(0\ 0\ 0\ A^{(1)}\ 0)$, $(0\ 0\ 0\ 0\ A^{(1)})$
$d^{(2)}$	$(0\ A^{(2)}\ 0\ A^{(2)}\ 0)$	6	$(A^{(2)}\ 0\ A^{(2)}\ 0\ 0)$, $(A^{(2)}\ 0\ 0\ A^{(2)}\ 0)$, $(A^{(2)}\ 0\ 0\ 0\ A^{(2)})$, $(0\ A^{(2)}\ 0\ A^{(2)}\ 0)$, $(0\ A^{(2)}\ 0\ 0\ A^{(2)})$, $(0\ 0\ A^{(2)}\ 0\ A^{(2)})$
$d^{(3)}$	$(A^{(3)}\ 0\ A^{(3)}\ 0\ A^{(3)})$	1	$(A^{(3)}\ 0\ A^{(3)}\ 0\ A^{(3)})$
$d^{(4)}$	$(0\ B^{(4)}\ B^{(4)}\ 0\ 0)$	4	$(B^{(4)}\ B^{(4)}\ 0\ 0\ 0)$, $(0\ B^{(4)}\ B^{(4)}\ 0\ 0)$, $(0\ 0\ B^{(4)}\ B^{(4)}\ 0)$, $(0\ 0\ 0\ B^{(4)}\ B^{(4)})$
$d^{(5)}$	$(A^{(5)}\ 0\ B^{(5)}\ B^{(5)}\ 0)$	6	$(A^{(5)}\ 0\ B^{(5)}\ B^{(5)}\ 0)$, $(0\ A^{(5)}\ 0\ B^{(5)}\ B^{(5)})$, $(A^{(5)}\ 0\ 0\ B^{(5)}\ B^{(5)})$, $(B^{(5)}\ B^{(5)}\ 0\ A^{(5)}\ 0)$, $(B^{(5)}\ B^{(5)}\ 0\ 0\ A^{(5)})$, $(0\ B^{(5)}\ B^{(5)}\ 0\ A^{(5)})$
$d^{(6)}$	$(0\ C^{(6)}\ D^{(6)}\ C^{(6)}\ 0)$	3	$(0\ C^{(6)}\ D^{(6)}\ C^{(6)}\ 0)$, $(C^{(6)}\ D^{(6)}\ C^{(6)}\ 0\ 0)$, $(0\ 0\ C^{(6)}\ D^{(6)}\ C^{(6)})$
$d^{(7)}$	$(B^{(7)}\ B^{(7)}\ 0\ B^{(7)}\ B^{(7)})$	1	$(B^{(7)}\ B^{(7)}\ 0\ B^{(7)}\ B^{(7)})$
$d^{(8)}$	$(A^{(8)}\ 0\ C^{(8)}\ D^{(8)}\ C^{(8)})$	2	$(C^{(8)}\ D^{(8)}\ C^{(8)}\ 0\ A^{(8)})$, $(A^{(8)}\ 0\ C^{(8)}\ D^{(8)}\ C^{(8)})$
$d^{(9)}$	$(E^{(9)}\ F^{(9)}\ F^{(9)}\ E^{(9)}\ 0)$	2	$(E^{(9)}\ F^{(9)}\ F^{(9)}\ E^{(9)}\ 0)$, $(0\ E^{(9)}\ F^{(9)}\ F^{(9)}\ E^{(9)})$
$d^{(10)}$	$(G^{(10)}\ H^{(10)}\ I^{(10)}\ H^{(10)}\ G^{(10)})$	1	$(G^{(10)}\ H^{(10)}\ I^{(10)}\ H^{(10)}\ G^{(10)})$

Table 1: Classes of equivalent structures for Problem 2.1.

Moreover the values of the non-zero doses are given by:

$$A^{(i)} = -\frac{\delta^{(i)}}{\sigma^{(i)}}\,, \quad i = 1,2,3,5,8\,,$$

$$B^{(i)} = -\frac{\delta^{(i)}}{\sigma^{(i)} + \tau^{(i)}}\,, \quad i = 4,5,7\,,$$

$$C^{(i)} = -\frac{\delta^{(i)}\left[\sigma^{(i)} - \tau^{(i)}\right]}{(\sigma^{(i)})^2 - 2(\tau^{(i)})^2}\,, \quad i = 6,8\,,$$

$$D^{(i)} = -\frac{\delta^{(i)}\left[\sigma^{(i)} - 2\tau^{(i)}\right]}{(\sigma^{(i)})^2 - 2(\tau^{(i)})^2}\,, \quad i = 6,8\,,$$

$$E^{(9)} = -\frac{\delta^{(9)}\sigma^{(9)}}{(\sigma^{(9)})^2 + \sigma^{(9)}\tau^{(9)} - (\tau^{(9)})^2}\,,$$

$$F^{(9)} = -\frac{\delta^{(9)}\left[\sigma^{(9)} - \tau^{(9)}\right]}{(\sigma^{(9)})^2 + \sigma^{(9)}\tau^{(9)} - (\tau^{(9)})^2}\,,$$

$$G^{(10)} = -\frac{\delta^{(10)}\left[(\sigma^{(10)})^2 - \sigma^{(10)}\tau^{(10)} - (\tau^{(10)})^2\right]}{\sigma^{(10)}\left[(\sigma^{(10)})^2 - 3(\tau^{(10)})^2\right]}\,,$$

$$H^{(10)} = -\frac{\delta^{(10)}\left[\sigma^{(10)} - 2\tau^{(10)}\right]}{(\sigma^{(10)})^2 - 3(\tau^{(10)})^2}\,,$$

$$I^{(10)} = -\frac{\delta^{(10)}\left[\sigma^{(10)} - \tau^{(10)}\right]^2}{\sigma^{(10)}\left[(\sigma^{(10)})^2 - 3(\tau^{(10)})^2\right]}\,,$$

with

$$\delta^{(i)} = \delta\left(\lambda^{(i)}\right)\,, \quad \sigma^{(i)} = \sigma\left(\lambda^{(i)}\right)\,, \quad \tau^{(i)} = \tau\left(\lambda^{(i)}\right)\,, \quad i = 1,\ldots,10\,,$$

and $\lambda^{(i)}$ is the fixed value of the multiplier λ associated to the i-th class of solutions $d^{(i)}$ and of related multipliers $\eta^{(i)}$.

Proof Using the definitions (3.9) we rewrite equations (3.2) - (3.4) in terms of δ, σ and τ. Multiplying each equation $\dfrac{\partial L}{\partial d_i} = 0$ given in (3.2) - (3.4) by the corresponding dose d_i, $i = 1,\ldots,5$, in view of (3.5) we get:

$$d_1[\delta(\lambda) + \sigma(\lambda)d_1 + \tau(\lambda)d_2] = 0\,,$$

$$d_i[\delta(\lambda) + \sigma(\lambda)d_i + \tau(\lambda)(d_{i-1} + d_{i+1})] = 0\,, \quad i = 2, 3, 4\,,$$

$$d_5[\delta(\lambda) + \sigma(\lambda)d_5 + \tau(\lambda)d_4] = 0\,.$$

This is a system of five non linear equations in five unknown variables. It may be solved sequentially starting for instance from the first equation. At the first step, we obtain two solutions for d_1 possibly depending on d_2:

$$d_1 = 0\,, \qquad d_1 = -\frac{\delta(\lambda)}{\sigma(\lambda)} - \frac{\tau(\lambda)}{\sigma(\lambda)}d_2\,.$$

At the second step, substituting these two values into the second equation, we get four values for d_2 possibly depending on d_3. Proceeding in the same way, at the 5th step we have 2^5 values for d_5. Substituting backward the obtained values, we arrive to 2^5 possible structures for the solution d, obviously depending on λ. These solutions can be grouped into the 10 classes reported in Table 1. Coming back to equations (3.2) - (3.4) and substituting the obtained values of the vector d, it is immediate to deduce the corresponding vectors of multipliers η. □

We remark that the trivial null vector $d = 0$ cannot be a solution, because it does not satisfy the constraint (3.6).

Because of the equivalence of all the structures belonging to the same class, in the following we consider a single structure as representative of the corresponding class. Therefore, from Theorem 3.1 we have only 10 different structures for the possible solutions d, As yet, the vectors d just classified in Theorem 3.1 are only candidates to be extremals of Problem 2.1 because the non negativity of η_i, $i = 1, \ldots, 5$, need to be to verified. In fact, in order to actually determine the optimal solutions of Problem 2.1, the multiplier λ has to be computed from the necessary conditions (3.6) and the obtained value has to be substituted into the vectors d and η verifying that they are non-negative. Then the solutions d so obtained are the extremals of Problem 2.1, that is all the possible candidates to give the optimal solution of the problem. Finally, the optimal solution can be determined by computing the cost function J for all the above extremals. Obviously, the optimal solution can be a multiple solution when it is provided by a class containing more than one equivalent structure. All the steps outlined above can be numerically performed once the model parameters are known.

We are going to give an analytical characterization of the optimal solution in terms of the new model parameters, that is the late tissue parameters ρ_l, γ_l, k_l and Q. In particular we find that Q acts as a switch for the optimal solution structure or in other words for the optimal number of positive doses per week. Moreover, for some Q values, the optimal dose size depends on the normal tissue parameters only.

4 How the optimum changes when Q changes.

We study the optimal solution of Problem 2.1 when Q changes by specializing the necessary and admissibility conditions (3.2) - (3.8) for each class of Table 1 and we show that the structure of the optimal solution depends only on the global parameter Q. In particular, the solution structure is invariant in the following four intervals of Q:

i) $Q \in (-\infty, 0)$,

ii) $Q = 0$,

iii) $Q \in (0, \overline{Q}]$,

iv) $Q \in (\overline{Q}, +\infty)$,

where

$$\overline{Q} = \frac{\sqrt{\rho_l^2 + \frac{4}{3}k_l}}{1 - 2\mathrm{e}^{-\gamma_l}} \,. \tag{4.1}$$

As for the optimal dose sizes, we find that they only depend on the late tissue parameters in the first three intervals i)-iii), whereas they depend on Q besides the late tissue parameters in interval iv). In order to prove the results of this section, let us rewrite the system of conditions (3.2) - (3.8) in its final form:

$$-Q + d_2 + \lambda(2d_1 + \rho_l + 2\mathrm{e}^{-\gamma_l} d_2) - \eta_1 = 0\,, \tag{4.2}$$

$$-Q + d_{i-1} + d_{i+1} + \lambda[2d_i + \rho_l + 2\mathrm{e}^{-\gamma_l}(d_{i-1} + d_{i+1})] - \eta_i = 0\,, \quad i = 2, 3, 4\,, \tag{4.3}$$

$$-Q + d_4 + \lambda(2d_5 + \rho_l + 2\mathrm{e}^{-\gamma_l} d_4) - \eta_5 = 0\,, \tag{4.4}$$

$$\rho_l \sum_{i=1}^{5} d_i + \sum_{i=1}^{5} d_i^2 + 2\mathrm{e}^{-\gamma_l} \sum_{i=2}^{5} d_{i-1} d_i - k_l = 0\,, \tag{4.5}$$

$$\eta_i d_i = 0\,, \quad i = 1, \ldots, 5\,, \tag{4.6}$$

$$d_i \geq 0\,, \quad \eta_i \geq 0\,, \quad i = 1, \ldots, 5\,. \tag{4.7}$$

In the following four subsections we separately report the results concerning the optimal solution in each of the mentioned four intervals of Q.

4.1 Optimal solution for Q < 0.

The present section concerns slowly proliferating tumours, that is tumours having $\rho < \rho_l$.

Theorem 4.1 *For $Q < 0$ the unique optimal solution is $d^{(1)}$ with:*

$$A^{(1)} = A_l^{(1)} = -\frac{\rho_l}{2} + \sqrt{\left(\frac{\rho_l}{2}\right)^2 + k_l} \,. \tag{4.8}$$

Proof For $Q < 0$ the class of solutions $d^{(1)}$ satisfies all the necessary conditions (4.2)-(4.7). Indeed, for the structure $d^{(1)}$ the equation (4.5) becomes:

$$\left(A^{(1)}\right)^2 + \rho_l A^{(1)} - k_l = 0 \,,$$

that has a unique positive root $A^{(1)} = A_l^{(1)}$, as in (4.8), and then $\eta_1 = 0$ from the complementarity conditions (4.6). It remains to verify the non negativity of η_i, $i = 2, \ldots, 5$. From (4.2) we have

$$\lambda = \frac{Q}{2A_l^{(1)} + \rho_l} \,, \tag{4.9}$$

and (4.3), (4.4) reduce to:

$$\eta_2 = -Q + A_l^{(1)} + \lambda \left(\rho_l + 2\mathrm{e}^{-\gamma_l} A_l^{(1)}\right) \,, \tag{4.10}$$

$$\eta_i = -Q + \lambda \rho_l \,, \quad i = 3, 4, 5 \,. \tag{4.11}$$

By substituting the expression (4.9) of λ in (4.10) and (4.11), it is easy to verify that

$$\eta_2 = A_l^{(1)} - Q \frac{2A_l^{(1)} \left(1 - 2\mathrm{e}^{-\gamma_l}\right)}{\left(2A_l^{(1)} + \rho_l\right)} \geq 0 \,, \tag{4.12}$$

$$\eta_i = -Q \frac{2A_l^{(1)}}{\left(\rho_l + 2\mathrm{e}^{-\gamma_l} A_l^{(1)}\right)} \geq 0 \,, \quad i = 3, 4, 5 \,, \tag{4.13}$$

if and only if $Q < 0$ (current interval of interest) or $Q = 0$ and for $\gamma_l > \ln(2)$, which is in agreement with γ_l values reported in literature [19] (see Section 2). Let us denote by $\mathcal{D}^{(i)}$ the total dose of the class $d^{(i)}$. For the class $d^{(1)}$ the equation (4.5) becomes

$$\left(\mathcal{D}^{(1)}\right)^2 + \rho_l \mathcal{D}^{(1)} - k_l = 0 \,,$$

whereas for any other class it becomes

$$\left(\mathcal{D}^{(i)}\right)^2 + \rho_l \mathcal{D}^{(i)} - k_l = 2 \sum_{i=2}^{5} \sum_{j=1}^{i-2} d_{i-1} d_i + 2\left(1 - \mathrm{e}^{-\gamma_l}\right) \sum_{i=2}^{5} d_{i-1} d_i > 0, \quad i = 2, 3, \ldots, 10 \,.$$

Hence, it can be easily seen that

$$\mathcal{D}^{(1)} < \mathcal{D}^{(i)}\,, \quad i = 2, 3, \ldots, 10\,.$$

Then, for the cost function, it is

$$J(d^{(1)}) = -Q\mathcal{D}^{(1)} < -Q\mathcal{D}^{(i)} < -Q\mathcal{D}^{(i)} + \sum_{i=2}^{5} d_{i-1}d_i = J(d^{(i)}), \quad i = 2, 3, \ldots, 10\,,$$

which proves the optimality of $d^{(1)}$, regardless of the actual existence of extremals in the classes $d^{(i)}$, $i = 2, 3, \ldots, 10$. □

4.2 Optimal solutions for Q = 0.

The optimal solutions provided by the theorem in the present section hold only in the limit condition of a tumour parameter ρ coincident with the normal tissue parameter ρ_l.

Theorem 4.2 *For $Q = 0$ there are three optimal solutions $d^{(i)}$, $i = 1, 2, 3$ with:*

$$A^{(i)} = A_l^{(i)} = -\frac{\rho_l}{2} + \sqrt{\left(\frac{\rho_l}{2}\right)^2 + \frac{k_l}{i}}\,, \; i = 1, 2, 3\,. \tag{4.14}$$

Proof For $Q = 0$ the classes of solutions $d^{(i)}$, $i = 1, 2, 3$, satisfy all the necessary conditions (4.2)-(4.7). To prove this statement, by substituting the structure $d^{(i)}$ into equation (4.5) we get:

$$i\left(A^{(i)}\right)^2 + i\rho_l A^{(i)} - k_l = 0\,, \quad i = 1, 2, 3\,,$$

that has a unique positive root $A^{(i)} = A_l^{(i)}$, $i = 1, 2, 3$, as in (4.14). The vectors $d^{(i)}$, $i = 1, 2, 3$, can only have either isolated positive or zero entries, so that we can denote by $\mathcal{I}_p$ the set of i positive entry indexes and $\mathcal{I}_z$ the set of $5 - i$ zero entry indexes. For $j \in \mathcal{I}_p$ it is $d_j^{(i)} = A_l^{(i)}$ and, from (4.6), $\eta_j^{(i)} = 0$. For $j \in \mathcal{I}_z$, it is $d_j^{(i)} = 0$ and it remains to verify $\eta_j^{(i)} \geq 0$. By substituting $d^{(i)}$, $\eta^{(i)}$, $i = 1, 2, 3$, in equations (4.2)-(4.4) we obtain i equations like the following one:

$$\lambda\left(2A_l^{(i)} + \rho_l\right) = 0\,,$$

that implies $\lambda = 0$. Setting $\lambda = 0$ into the remaining $5 - i$ equations gives:

$$\eta_j^{(i)} = \left(d_{j-1}^{(i)} + d_{j+1}^{(i)}\right)\,, \quad j \in \mathcal{I}_z\,.$$

Clearly it is $\eta_j^{(i)} \geq 0$, $j \in \mathcal{I}_z$, which proves the admissibility of the extremals $d^{(i)}$, $i = 1, 2, 3$.

Moreover, it is $J(d^{(i)}) = 0$, $i = 1, 2, 3$, whereas $J(d^{(i)})$, $i = 4, 5, \ldots, 10$, are strictly positive since they contain at least one interaction term. □

We remark that the condition $Q = 0$ ($\rho = \rho_l$), giving three optimal solutions for Problem 2.1, must be considered as a limit case because the tumour and normal tissues are indistinguishable. Actually, for $i = 1, 2, 3$, $J(d^{(i)})$ do not contain the interaction terms $\tilde{E}_2$ given in Eq. (2.4) and then it is $J(d^{(i)}) \equiv 0$.

4.3 Optimal solution for $\mathbf{0 < Q \leq \overline{Q}}$.

The optimal solution provided by the following theorem is valid for tumours having $\rho > \rho_l$, provided that the pair of tumour parameters ρ, γ be such that $Q \leq \overline{Q}$.

Theorem 4.3 *For $Q \in (0, \overline{Q}]$ the unique optimal solution is $d^{(3)}$ with:*

$$A^{(3)} = A_l^{(3)} = -\frac{\rho_l}{2} + \sqrt{\left(\frac{\rho_l}{2}\right)^2 + \frac{k_l}{3}} \,. \tag{4.15}$$

Proof First of all, we introduce a further expression for $\overline{Q}$ in terms of $A_l^{(3)}$ that turns out to be useful for the following proofs. We have:

$$\overline{Q} = \frac{2A_l^{(3)} + \rho_l}{1 - 2\mathrm{e}^{-\gamma_l}} \,, \tag{4.16}$$

easily obtained from (4.1) and using the expression of $A_l^{(3)}$ in (4.15).

For $Q \in (0, \overline{Q}]$, again we prove that the solution $d^{(3)}$ satisfies all the necessary conditions (4.2)-(4.7). Indeed, for the structure $d^{(3)}$ the equation (4.5) becomes:

$$3\left(A^{(3)}\right)^2 + 3\rho_l A^{(3)} - k_l = 0 \,, \tag{4.17}$$

that has a unique positive root $A^{(3)} = A_l^{(3)}$, as in (4.15), and then $\eta_1 = \eta_3 = \eta_5 = 0$. It remains to verify the non negativity of η_2, η_4. From (4.2), for instance, we have

$$\lambda = \frac{Q}{2A_l^{(3)} + \rho_l} \,, \tag{4.18}$$

and equations in (4.3), for $i = 2, 4$, reduce to:

$$\eta_2 = \eta_4 = -Q + 2A_l^{(3)} + \lambda\left(\rho_l + 4\mathrm{e}^{-\gamma_l} A_l^{(3)}\right) \,. \tag{4.19}$$

By substituting the expression (4.18) of λ in (4.19), it is easy to verify that

$$\eta_2 = \eta_4 = 2A_l^{(3)}\left(1 - Q\frac{1 - 2\mathrm{e}^{-\gamma_l}}{2A_l^{(3)} + \rho_l}\right) \geq 0 \,, \tag{4.20}$$

if and only if $Q \leq \overline{Q}$, with $\overline{Q}$ given by (4.16), and for $\gamma_l > \ln(2)$.

To prove the optimality of $d^{(3)}$ we must verify that $J(d^{(i)})$ is greater than $J(d^{(3)})$, for $i \neq 3$.

I) $\boldsymbol{J\left(d^{(3)}\right) < J\left(d^{(i)}\right),\ i = 1,\ldots,6}$.

We start proving that for classes $d^{(i)}$, $i = 1,\ldots,6$ it is

$$\mathcal{D}^{(3)} > \mathcal{D}^{(i)}\,, \quad i = 1,\ldots,6\,, \quad i \neq 3\,. \tag{4.21}$$

Since the vectors of these classes always have at least two zero doses, we can rewrite the constraint (4.5) using a lower number of variables, three instead of five, namely $x, y, z \geq 0$. All the obtained 3-D constraints can be represented in a compact form by the following family of surfaces:

$$x^2 + y^2 + z^2 + \rho_l(x+y+z) + h_1(i)2\mathrm{e}^{-\gamma_l}xy + h_2(i)2\mathrm{e}^{-\gamma_l}yz - k_l = 0\,, \quad i = 1,\ldots,6\,, \tag{4.22}$$

where

$$h_1(i) = \begin{cases} 1\,, & i = 4,6\,, \\ \\ 0\,, & i = 1,2,3,5\,, \end{cases} \qquad\qquad h_2(i) = \begin{cases} 1\,, & i = 5,6\,, \\ \\ 0\,, & i = 1,\ldots,4\,. \end{cases}$$

It is easy to see that substituting the six points (representative of the six classes),

$$\begin{pmatrix} A^{(1)} & 0 & 0 \end{pmatrix}, \quad \begin{pmatrix} A^{(2)} & A^{(2)} & 0 \end{pmatrix}, \quad \begin{pmatrix} A^{(3)} & A^{(3)} & A^{(3)} \end{pmatrix},$$

$$\begin{pmatrix} B^{(4)} & B^{(4)} & 0 \end{pmatrix}, \quad \begin{pmatrix} A^{(5)} & B^{(5)} & B^{(5)} \end{pmatrix}, \quad \begin{pmatrix} C^{(6)} & D^{(6)} & C^{(6)} \end{pmatrix}\,,$$

into (4.22) we re-obtain the constraint (4.5) for each structure $d^{(i)}$, $i = 1,\ldots,6$.

Let us consider now the sphere in R^3

$$S = \left\{(x,y,z) \in R^3 |\ \ x^2 + y^2 + z^2 + \rho_l(x+y+z) - k_l = 0\right\}\,,$$

noting that S contains the surfaces of the family (4.22), since $h_1(i)2\mathrm{e}^{-\gamma_l}xy + h_2(i)2\mathrm{e}^{-\gamma_l}yz \geq 0$. Moreover, it can be verified that

$$x + y + z \leq \mathcal{D}^{(3)} = 3A_l^{(3)}\,. \tag{4.23}$$

This property can be proved considering the minimum problem

$$\min_{(x,y,z)\in S} \{-(x+y+z)\}\,,$$

that is a convex problem for which the classical sufficient conditions of optimality apply and give the unique (uniform) solution

$$x = y = z = A_l^{(3)}\,.$$

Therefore, all the points (x,y,z) on the surfaces (4.22) verify (4.23) and the property (4.21) holds. In conclusion, for the classes $d^{(i)}$, $i = 1,\ldots,6$, it is

$$J(d^{(i)}) = -Q\mathcal{D}^{(i)} + \sum_{i=2}^{5} d_{i-1}d_i > -Q\mathcal{D}^{(i)} > -Q\mathcal{D}^{(3)} = J(d^{(3)}), \quad i = 1,\ldots,6\,, \quad i \neq 3\,.$$

II) $\boldsymbol{J}\left(\boldsymbol{d}^{(3)}\right) < \boldsymbol{J}\left(\boldsymbol{d}^{(7)}\right)$.

Let us consider the class $d^{(7)}$. Equation (4.5) becomes:

$$4\left(1+\mathrm{e}^{-\gamma_l}\right)\left(B^{(7)}\right)^2 + 4\rho_l B^{(7)} - k_l = 0\,, \tag{4.24}$$

that has the unique positive root

$$B^{(7)} = B_l^{(7)} = \frac{1}{1+\mathrm{e}^{-\gamma_l}}\left[-\frac{\rho_l}{2} + \sqrt{\left(\frac{\rho_l}{2}\right)^2 + \frac{k_l}{4/\left(1+\mathrm{e}^{-\gamma_l}\right)}}\right].$$

The related multipliers are $\eta_1 = \eta_2 = \eta_4 = \eta_5 = 0$ and it remains to verify the non negativity of η_3. By specializing the necessary conditions to $d^{(7)}$, Eq. (4.2), for instance, yields

$$\lambda = \frac{Q - B_l^{(7)}}{2\left(1+\mathrm{e}^{-\gamma_l}\right)B_l^{(7)} + \rho_l}\,, \tag{4.25}$$

and equation (4.3) for $i = 3$ reduces to:

$$\eta_3 = -Q + 2B_l^{(7)} + \lambda\left(\rho_l + 4\mathrm{e}^{-\gamma_l}B_l^{(7)}\right)\,. \tag{4.26}$$

By substituting the expression (4.25) of λ in (4.26), we see that

$$\eta_3 = B_l^{(7)}\frac{\rho_l + 4B_l^{(7)} - 2Q\left(1-\mathrm{e}^{-\gamma_l}\right)}{2\left(1+\mathrm{e}^{-\gamma_l}\right)B_l^{(7)} + \rho_l} \geq 0\,, \tag{4.27}$$

if and only if

$$Q \leq \frac{\rho_l + 4B_l^{(7)}}{2\left(1-\mathrm{e}^{-\gamma_l}\right)} \triangleq Q_7\,. \tag{4.28}$$

So it is enough to show that, for $Q \in (0, Q_7]$,

$$J(d^{(7)}) > J(d^{(3)})\,. \tag{4.29}$$

The cost functions

$$J(d^{(3)}) = -3QA_l^{(3)}$$

and

$$J(d^{(7)}) = -4QB_l^{(7)} + 2\left(B_l^{(7)}\right)^2\,,$$

are linearly decreasing functions of Q with angular coefficients $-3A_l^{(3)}$ and $-4B_l^{(7)}$ respectively. The linearity of $J(d^{(3)})$ and $J(d^{(7)})$ allows us to verify the property (4.29) only for $Q = 0$ and $Q = Q_7$. In $Q = 0$, (4.29) is obviously satisfied because it reduces to

$$2\left(B_l^{(7)}\right)^2 > 0\,.$$

Coming to $Q = Q_7$ we have to distinguish two cases. If $3A_l^{(3)} > 4B_l^{(7)}$ the property (4.29) is trivially verified in the whole interval $(0, Q_7]$. Let then $3A_l^{(3)} < 4B_l^{(7)}$. We have to verify (4.29) at $Q = Q_7$, that is

$$4B_l^{(7)} \left[\frac{\rho_l + 4B_l^{(7)}}{(1 - \mathrm{e}^{-\gamma_l})} - B_l^{(7)} \right] < 3A_l^{(3)} \frac{\rho_l + 4B_l^{(7)}}{(1 - \mathrm{e}^{-\gamma_l})} \,. \tag{4.30}$$

From the constraints (4.17) and (4.24) we get the equality

$$\frac{4B_l^{(7)}}{3A_l^{(3)}} = \frac{A_l^{(3)} + \rho_l}{(1 + \mathrm{e}^{-\gamma_l})\, B_l^{(7)} + \rho_l} \,,$$

that substituted in (4.30) gives

$$\left(3 + \mathrm{e}^{-\gamma_l}\right) A_l^{(3)} B_l^{(7)} + \rho_l A_l^{(3)} < 4 \left(1 + \mathrm{e}^{-\gamma_l}\right) \left(B_l^{(7)}\right)^2 + 2\rho_l B_l^{(7)} \,. \tag{4.31}$$

The latter inequality is true when $3A_l^{(3)} < 4B_l^{(7)}$, which means that the property (4.29) holds.

III) $\boldsymbol{J\left(d^{(3)}\right) < J\left(d^{(8)}\right)}$.

The next class to deal with is $d^{(8)}$. Solutions in this class have three (non-negative) unknowns and then we consider the first octant of the three-dimensional space ($A^{(8)}$, $C^{(8)}$, $D^{(8)}$). The solution points must satisfy the constraint

$$\left(A^{(8)}\right)^2 + 2\left(C^{(8)}\right)^2 + \left(D^{(8)}\right)^2 + \rho_l \left(A^{(8)} + 2C^{(8)} + D^{(8)}\right) + 4\mathrm{e}^{-\gamma_l} C^{(8)} D^{(8)} - k_l = 0 \,, \tag{4.32}$$

and the necessary conditions (4.2)-(4.4). In particular, Eq. (4.4) becomes

$$-Q + \lambda \left(2A^{(8)} + \rho_l\right) = 0 \,, \tag{4.33}$$

and straightaway implies $\lambda > 0$ for $Q > 0$. The argument that follows aims at reducing the region where extremals can be found, so to reduce the region where we have to check $J(d^{(8)}) > J(d^{(3)})$, or the non-optimality of $d^{(8)}$. Instead of writing the remaining necessary conditions, it is convenient to consider the differences between pairs of conditions (4.2)-(4.4) and deduce further expressions of λ. We have

$$\begin{aligned} \lambda &= \frac{D^{(8)}}{2\left(A^{(8)} - C^{(8)} - \mathrm{e}^{-\gamma_l} D^{(8)}\right)} = \\ &= \frac{C^{(8)}}{A^{(8)} - D^{(8)} - 2\mathrm{e}^{-\gamma_l} C^{(8)}} = \\ &= \frac{D^{(8)} - 2C^{(8)}}{2\left(D^{(8)} - C^{(8)} - \mathrm{e}^{-\gamma_l}(D^{(8)} - 2C^{(8)})\right)} \,. \end{aligned} \tag{4.34}$$

At first, let $C^{(8)}$, $D^{(8)}$ be positive. To guarantee $\lambda > 0$, the first two expressions in (4.34) require

$$A^{(8)} > C^{(8)} + \mathrm{e}^{-\gamma_l} D^{(8)} > C^{(8)}\,, \qquad A^{(8)} > D^{(8)} + 2\mathrm{e}^{-\gamma_l} C^{(8)} > D^{(8)}\,, \tag{4.35}$$

while from the third expression (4.34) we get two alternatives:

$$D^{(8)} < C^{(8)} \quad \text{or} \quad D^{(8)} > 2C^{(8)}\,. \tag{4.36}$$

Let us now suppose $C^{(8)} = 0$ or $D^{(8)} = 0$. From (4.34), (4.32) and (4.33) it can be seen that only two points are consistent with the condition $\lambda > 0$:

$$P_2 = \begin{pmatrix} A_l^{(2)} \\ 0 \\ A_l^{(2)} \end{pmatrix}, \qquad Q = \frac{\rho_l + 2A_l^{(2)}}{2\,(1-\mathrm{e}^{-\gamma_l})} \triangleq Q_2\,, \tag{4.37}$$

and

$$P_3 = \begin{pmatrix} A_l^{(3)} \\ A_l^{(3)} \\ 0 \end{pmatrix}, \qquad Q = \overline{Q}\,. \tag{4.38}$$

Figure 1 illustrates the two admissible subregions on the ellipsoid (4.32) defined by (4.35) and (4.36): region $\mathcal{A}$, where $D^{(8)} > 2C^{(8)}$, and region $\mathcal{B}$, where $D^{(8)} < C^{(8)}$. Possible extremals $d^{(8)}$ cannot lie outside $\mathcal{A}$ or $\mathcal{B}$ for $Q > 0$. Anyway, the solutions $d^{(8)}$ must satisfy, besides the constraint (4.32), two out of the three following equations:

$$4\left(C^{(8)}\right)^2 - 2\left(D^{(8)}\right)^2 + \rho_l\left(2C^{(8)} - D^{(8)}\right) - 2Q\left[\left(1-2\mathrm{e}^{-\gamma_l}\right)C^{(8)} - \left(1-\mathrm{e}^{-\gamma_l}\right)D^{(8)}\right] = 0\,, \tag{4.39}$$

$$2A^{(8)}C^{(8)} + \rho_l C^{(8)} - Q\left[A^{(8)} - 2\mathrm{e}^{-\gamma_l}C^{(8)} - D^{(8)}\right] = 0\,, \tag{4.40}$$

$$2A^{(8)}D^{(8)} + \rho_l D^{(8)} - 2Q\left[A^{(8)} - C^{(8)} - \mathrm{e}^{-\gamma_l}D^{(8)}\right] = 0\,, \tag{4.41}$$

obtained, as done for previous cases, by writing (4.2)-(4.4) for the structure $d^{(8)}$ and eliminating λ. Furthermore, by exploiting (4.39)-(4.41) (in particular (4.39) + (4.41) $-$ 2 $\times$ (4.40)) we get the equation of another surface (independent of Q), where solutions $d^{(8)}$ must necessarily lie (Fig. 2):

$$2\left(C^{(8)}\right)^2 - \left(D^{(8)}\right)^2 + A^{(8)}(D^{(8)} - 2C^{(8)}) = 0\,. \tag{4.42}$$

The intersection between the hyperboloid (4.42) and the ellipsoid (4.32) consists of two connected arcs of regular curve, $\mathcal{C}_8' \subset \mathcal{A}$ and $\mathcal{C}_8'' \subset \mathcal{B}$, as shown in Fig. 3. For each Q, the real positive solutions are points $P(Q) = \left(A^{(8)}(Q), C^{(8)}(Q), D^{(8)}(Q)\right)^T$ determined on $\mathcal{C}_8' \cup \mathcal{C}_8''$ by the intersection with one of the surfaces (4.39)-(4.41). The solution path along $\mathcal{C}_8'$ starts from point

$$P_1 = \begin{pmatrix} A_l^{(1)} \\ 0 \\ 0 \end{pmatrix}$$

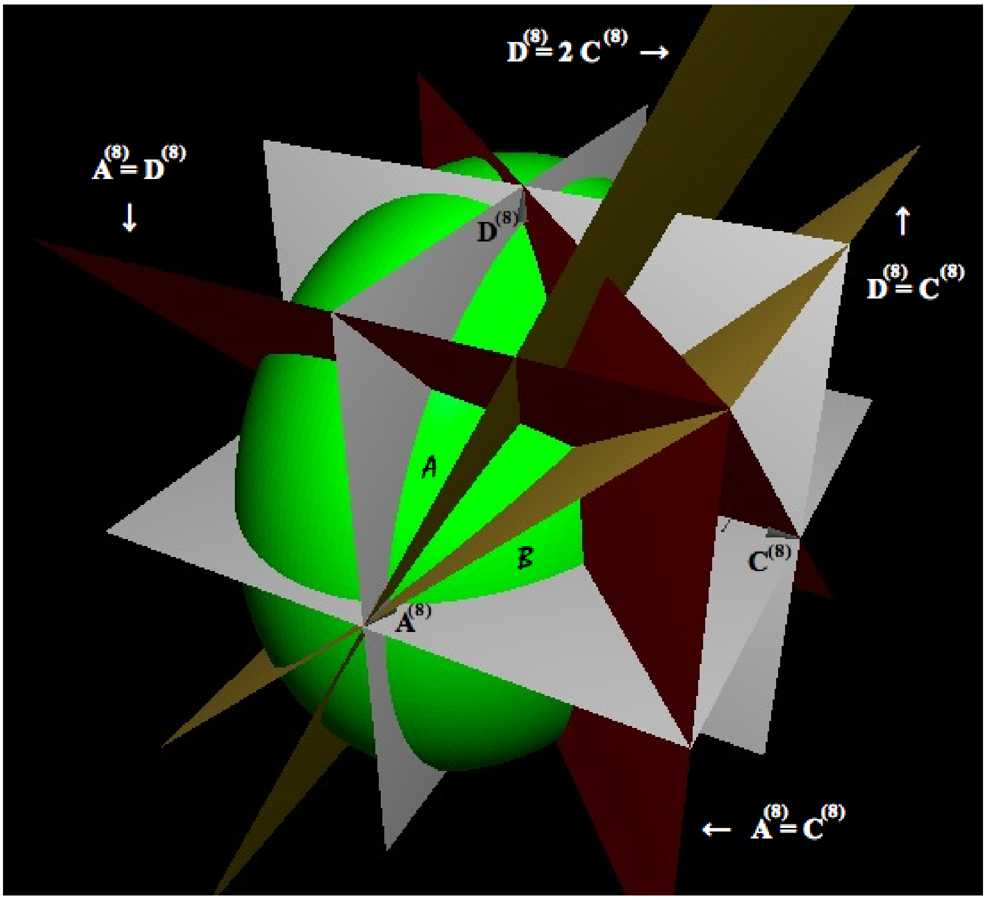

Figure 1: Admissible subregions $\mathcal{A}$ and $\mathcal{B}$ on the ellipsoid (4.32) for the solution $d^{(8)}$.

for $Q = 0$ (as it is easily seen setting $Q = 0$ in Eqs. (4.40), (4.41) and using (4.32)) and reaches point P_2 for $Q = Q_2$ (see Eq. (4.37)). Similarly, the solution path along $\mathcal{C}_8''$ starts from point P_3 in (4.38) for $Q = \overline{Q}$ and tends in the limit $Q \to \infty$ to the point P_∞:

$$
\begin{aligned}
A_\infty^{(8)} &= a\, D_\infty^{(8)}\,, \\
C_\infty^{(8)} &= b\, D_\infty^{(8)}\,, \\
D_\infty^{(8)} &= \frac{h_n(a,b)}{h_d(a,b)} \left[-\frac{\rho_l}{2} + \sqrt{\left(\frac{\rho_l}{2}\right)^2 + \frac{h_d(a,b)}{h_n^2(a,b)}\, k_l}\, \right],
\end{aligned}
$$

where $h_n(a,b) = 1 + a + 2b$ and $h_d(a,b) = 1 + a^2 + 2b^2 + 4\mathrm{e}^{-\gamma_l} b$, with $a = \dfrac{1 - 2\mathrm{e}^{-2\gamma_l}}{1 - 2\mathrm{e}^{-\gamma_l}}$ and $b = \dfrac{1 - \mathrm{e}^{-\gamma_l}}{1 - 2\mathrm{e}^{-\gamma_l}}$. The coordinates of P_∞ can be found using the constraint (4.32) and taking the limit $Q \to \infty$ in Equations (4.39) and (4.40).

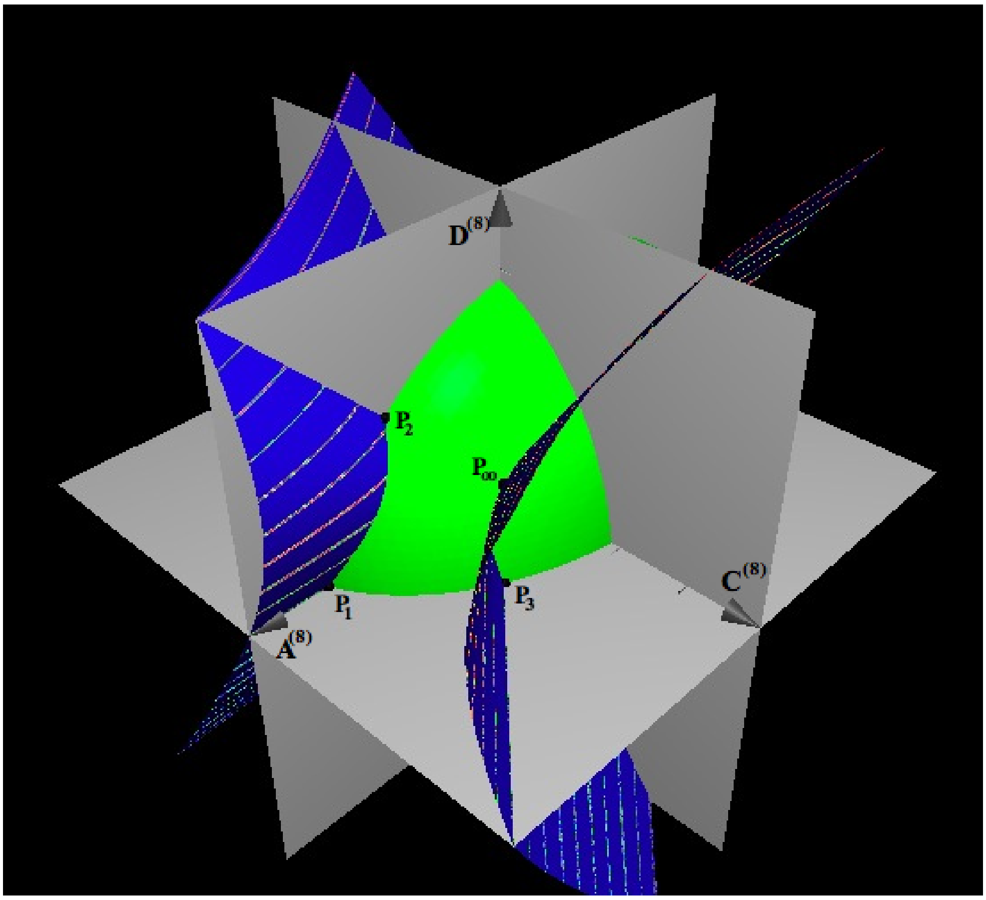

Figure 2: Hyperboloid (4.42) and ellipsoid (4.32) whose intersection contains the admissible solutions $d^{(8)}$.

A useful property that we are going to show is that not only each point $P(Q)$ is associated to a single value of Q (evident from the linearity in Q of Equations (4.39)-(4.41)), but also each value of Q, $Q \in (0, Q_2] \cup [\overline{Q}, +\infty]$, is associated to a unique point $P(Q)$. First of all, we stress that points P_1 and P_∞ are attained for a unique value of Q, as outlined above. We show the solution uniqueness for the arc $\mathcal{C}_8'$ starting from P_1 and increasing Q from zero, but the same argument can be applied to show the solution uniqueness on $\mathcal{C}_8''$ starting from P_∞ and decreasing Q from $+\infty$. The solution $P(Q)$ moves continuously on $\mathcal{C}_8'$ in a single direction from P_1 to P_2. For any $Q' \in (0, Q_2]$, the point $P(Q')$ is the only real positive solution: if a different solution point $R(Q')$ existed on $\mathcal{C}_8'$, then two different points would exist on $\mathcal{C}_8'$ itself with the same value of Q'. As a consequence, a value $Q'' \in (0, Q_2]$, $Q'' \neq Q'$, would exist such that $P(Q'') \equiv R(Q')$, which is impossible in view of the linear dependence on Q of Equations (4.39)-(4.41).

Note that

$$Q_2 < \overline{Q}\,, \tag{4.43}$$

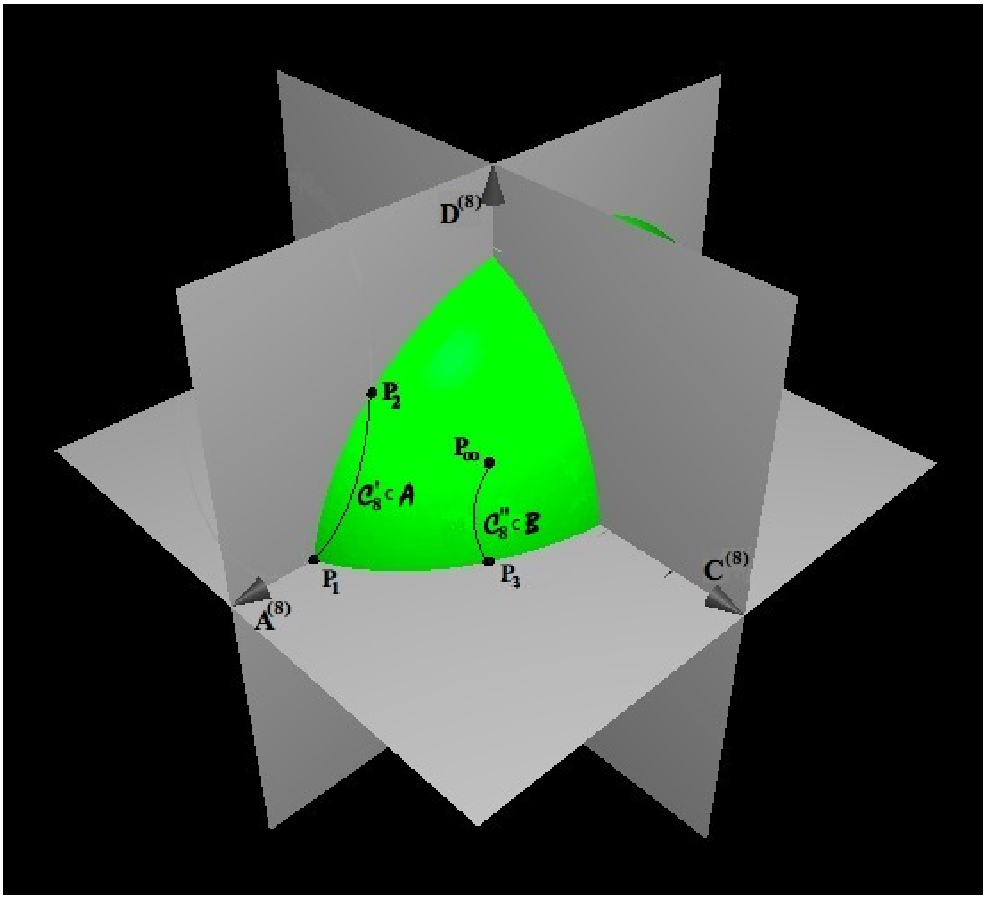

Figure 3: Regular curves $\mathcal{C}_8'$ and $\mathcal{C}_8''$, intersections between the hyperboloid (4.42) and the ellipsoid (4.32), containing the admissible solutions $d^{(8)}$.

as we can write

$$Q_2 = \frac{\rho_l + 2A_l^{(2)}}{2\,(1 - \mathrm{e}^{-\gamma_l})} < \frac{\rho_l + 3A_l^{(3)}}{2\,(1 - \mathrm{e}^{-\gamma_l})} < \frac{\rho_l + 2A_l^{(3)}}{1 - 2\mathrm{e}^{-\gamma_l}} = \overline{Q}\,, \tag{4.44}$$

where the first inequality is true since $\mathcal{D}^{(2)} < \mathcal{D}^{(3)}$ and the last is trivially true. In view of the uniqueness of the solution and of the property (4.43), no solution $d^{(8)}$ exists for $Q \in (Q_2, \overline{Q})$, while it is clear that $d^{(8)} \equiv d^{(3)}$ for $Q = \overline{Q}$. Therefore, we can consider only the path $\mathcal{C}_8' \subset \mathcal{A}$ (Fig. 3). For sake of simplicity, instead of $\mathcal{C}_8'$ we actually consider a subset of $\mathcal{A}$ that strictly contains $\mathcal{C}_8'$ itself. Such a subset is the intersection between the region $\mathcal{A}$ and the half-space

$$2C^{(8)} + D^{(8)} - A^{(8)} \leq 0\,, \tag{4.45}$$

since Eq. (4.42) when $D^{(8)} > 2C^{(8)}$ implies inequality (4.45). We can now prove that in this subset it is

$$J(d^{(8)}) = -Q\left(2C^{(8)} + D^{(8)} + A^{(8)}\right) + 2C^{(8)}D^{(8)} > -3QA_l^{(3)} = J(d^{(3)})\,, \tag{4.46}$$

or equivalently, being $C^{(8)}D^{(8)} \geq 0$,

$$\mathcal{D}^{(8)} = 2C^{(8)} + D^{(8)} + A^{(8)} < \mathcal{D}^{(3)} . \tag{4.47}$$

Let us denote by ℓ the arc of curve given by the intersection between $\mathcal{A}$ and the plane

$$2C^{(8)} + D^{(8)} - A^{(8)} = 0 , \tag{4.48}$$

and by $\ell^\star$ the intersection between $\mathcal{A}$ and the plane

$$A^{(8)} + 2C^{(8)} + D^{(8)} = \mathcal{D}^{(3)} . \tag{4.49}$$

From the geometric point of view, proving (4.47) means proving that ℓ entirely lies below the plane (4.49). First we show that the curves ℓ and $\ell^\star$ do not intersect with each other. Let us consider the system formed by planes (4.48) and (4.49) and the region $\mathcal{A}$:

$$\begin{cases} \left(A^{(8)}\right)^2 + 2\left(C^{(8)}\right)^2 + \left(D^{(8)}\right)^2 + \rho_l\left(A^{(8)}+2C^{(8)}+D^{(8)}\right)+4\mathrm{e}^{-\gamma_l}C^{(8)}D^{(8)} - k_l = 0 , \\ A^{(8)} \geq D^{(8)} , \\ D^{(8)} > 2C^{(8)} , \end{cases}$$

and let us solve it for example with respect to $C^{(8)}$. We get the roots

$$C^{(8)} = \frac{3\left(1-\mathrm{e}^{-\gamma_l}\right) \pm \sqrt{3\mathrm{e}^{-\gamma_l}\left(-2+3\mathrm{e}^{-\gamma_l}\right)}}{2\left(3-4\mathrm{e}^{-\gamma_l}\right)} A_l^{(3)} ,$$

that are complex roots, as $\gamma_l > \ln(2)$. Now, it suffices to verify that (4.47) is true in a single point of ℓ, say point P_2. Indeed, it is

$$A^{(8)} + 2C^{(8)} + D^{(8)} = 2A_l^{(2)} < \mathcal{D}^{(3)} ,$$

which proves (4.46).

IV) $\boldsymbol{J}\left(\boldsymbol{d}^{(3)}\right) < \boldsymbol{J}\left(\boldsymbol{d}^{(9)}\right)$.

Let us consider now the class $d^{(9)}$. Equation (4.5) becomes:

$$2\left(E^{(9)}\right)^2 + 2\left(1+\mathrm{e}^{-\gamma_l}\right)\left(F^{(9)}\right)^2 + 2\rho_l\left(E^{(9)}+F^{(9)}\right) + 4\mathrm{e}^{-\gamma_l}E^{(9)}F^{(9)} - k_l = 0 .$$

and it is easily seen that the late constraint limits $E^{(9)}$ to the maximum value $A_l^{(2)}$, attained when $F^{(9)} = 0$. The multipliers associated to $d^{(9)}$ are $\eta_1 = \eta_2 = \eta_3 = \eta_4 = 0$, while the non-negativity of η_5 can be verified by specializing the necessary conditions to $d^{(9)}$. From Eq. (4.3) for $i = 2$, we obtain an expression of λ that substituted in (4.4) gives

$$\eta_5 = F^{(9)} \frac{2E^{(9)} - \rho_l - 2Q\left(1+\mathrm{e}^{-\gamma_l}\right)}{2\left(1+\mathrm{e}^{-\gamma_l}\right)F^{(9)} + 2\mathrm{e}^{-\gamma_l}E^{(9)} + \rho_l} .$$

Then, $\eta_5 \geq 0$ if and only if

$$Q \leq \frac{2E^{(9)} - \rho_l}{2\,(1 + \mathrm{e}^{-\gamma_l})} \triangleq Q_9\,.$$

So it suffices to show

$$J(d^{(9)}) = -2Q\left(E^{(9)} + F^{(9)}\right) + 2E^{(9)}F^{(9)} + \left(F^{(9)}\right)^2 > J(d^{(3)}) = -3QA_l^{(3)}\,, \tag{4.50}$$

for $Q \in (0, Q_9]$.

Dividing both sides of (4.50) by Q and noting that $Q \leq Q_9 < E^{(9)}$, we have the inequalities

$$-2\left(E^{(9)} + F^{(9)}\right) + \frac{2E^{(9)}F^{(9)} + \left(F^{(9)}\right)^2}{Q} > E^{(9)}\left[\left(\frac{F^{(9)}}{E^{(9)}}\right)^2 - 2\right] > -3A_l^{(3)}\,.$$

Recalling that $E^{(9)} \leq A_l^{(2)}$, we get the further inequalities

$$E^{(9)}\left[\left(\frac{F^{(9)}}{E^{(9)}}\right)^2 - 2\right] \geq -2A_l^{(2)} > -3A_l^{(3)}\,.$$

This latter inequality is verified since $\mathcal{D}^{(2)} = 2A_l^{(2)} < \mathcal{D}^{(3)} = 3A_l^{(3)}$ (see (4.21)), so the proof related to class $d^{(9)}$ is complete.

II) $\boldsymbol{J\left(d^{(3)}\right) < J\left(d^{(10)}\right)}$.

The last class to be considered is $d^{(10)}$. Let us specialize the necessary conditions to the structure $d^{(10)}$. The conditions (4.2)-(4.4) reduce to the following:

$$-Q + H^{(10)} + \lambda(2G^{(10)} + \rho_l + 2\mathrm{e}^{-\gamma_l}H^{(10)}) = 0\,, \tag{4.51}$$

$$-Q + G^{(10)} + I^{(10)}) + \lambda[2H^{(10)} + \rho_l + 2\mathrm{e}^{-\gamma_l}(G^{(10)} + I^{(10)})] = 0\,, \tag{4.52}$$

$$-Q + 2H^{(10)} + \lambda(2I^{(10)} + \rho_l + 4\mathrm{e}^{-\gamma_l}H^{(10)}) = 0\,, \tag{4.53}$$

and the constraint (4.5) becomes:

$$2\left(G^{(10)}\right)^2 + 2\left(H^{(10)}\right)^2 + \left(I^{(10)}\right)^2 + \rho_l\left(2G^{(10)} + 2H^{(10)} + I^{(10)}\right) + \\ + 4\mathrm{e}^{-\gamma_l}H^{(10)}\left(G^{(10)} + I^{(10)}\right) - k_l = 0\,. \tag{4.54}$$

By expressing the multiplier λ in terms of the doses, we arrive to the following quadratic system of three equations in three unknown doses:

$$2\left(G^{(10)}\right)^2+2\left(H^{(10)}\right)^2+2G^{(10)}I^{(10)}+\rho_l\left(G^{(10)}-H^{(10)}+I^{(10)}\right)-\\ -2Q\left[\left(1-\mathrm{e}^{-\gamma_l}\right)G^{(10)}-\left(1-\mathrm{e}^{-\gamma_l}\right)H^{(10)}-\mathrm{e}^{-\gamma_l}I^{(10)}\right]=0\,, \tag{4.55}$$

$$H^{(10)}\left(4G^{(10)}-2I^{(10)}+\rho_l\right)-2Q\left[G^{(10)}-\mathrm{e}^{-\gamma_l}H^{(10)}-I^{(10)}\right]=0\,, \tag{4.56}$$

$$-4\left(H^{(10)}\right)^2+2\left(I^{(10)}\right)^2+2G^{(10)}I^{(10)}+\rho_l\left(G^{(10)}-2H^{(10)}+I^{(10)}\right)+\\ +2Q\left[\mathrm{e}^{-\gamma_l}G^{(10)}+\left(1-2\mathrm{e}^{-\gamma_l}\right)H^{(10)}-\left(1-\mathrm{e}^{-\gamma_l}\right)I^{(10)}\right]=0\,. \tag{4.57}$$

Let us consider the three-dimensional space $\left(G^{(10)}, H^{(10)}, I^{(10)}\right)$. The solution $d^{(10)}$ is given by the intersection of two out of the three surfaces (4.55)-(4.57) and the constraint (4.54) and it depends on Q. In order to characterize the solution, it is convenient to consider the simpler surface, not depending on Q, obtained by subtracting (4.57) from the sum between (4.55) and (4.56):

$$\left(I^{(10)}\right)^2-H^{(10)}I^{(10)}-\left(H^{(10)}-G^{(10)}\right)^2=0\,. \tag{4.58}$$

As depicted by Fig. 4, it is easy to see that the intersection between the cone (4.58) and the ellipsoid (4.54) in the first octant consists in a connected arc of regular curve $\mathcal{C}_{10}\subset(R^+)^3$ plus an isolated point P_2 (see Fig. 5). For each Q, the real positive solutions are points $P(Q)=\left(G^{(10)}(Q), H^{(10)}(Q), I^{(10)}(Q)\right)^T$ determined on $\mathcal{C}_{10}\cup\{P_2\}$ by the intersection with one of the surfaces (4.55)-(4.57). A useful property that we are going to show is that for any $Q\in(-\infty,+\infty)$ the solution $P(Q)$ is unique, while it is evident that each point $P(Q)$ is associated to a single value of Q (since Equations (4.55)-(4.57) are linear in Q). Let us characterize the set $\mathcal{C}_{10}\cup\{P_2\}$. The extreme points of $\mathcal{C}_{10}$ are:

$$P_1=\begin{pmatrix}0\\ \frac{\sqrt{5}-1}{2}\tilde{I}\\ \tilde{I}\end{pmatrix}, \qquad \text{for}\quad Q=\widetilde{Q}=\frac{\sqrt{5}-1}{2}\,\frac{2\tilde{I}-\rho_l}{1+\mathrm{e}^{-\gamma_l}(\sqrt{5}-1)/2}\,,$$

where $\tilde{I}$ is the positive root of

$$\left[4-\sqrt{5}+2\mathrm{e}^{-\gamma_l}\left(\sqrt{5}-1\right)\right]\left(I^{(10)}\right)^2+\rho_l\sqrt{5}I^{(10)}-k_l=0\,,$$

and

$$P_3=\begin{pmatrix}A_l^{(3)}\\ 0\\ A_l^{(3)}\end{pmatrix}, \qquad \text{for}\quad Q=\overline{Q}\,,$$

while the point P_2 is:

$$P_2=\begin{pmatrix}B_l^{(7)}\\ B_l^{(7)}\\ 0\end{pmatrix}, \qquad \text{for}\quad Q=Q_7\,.$$

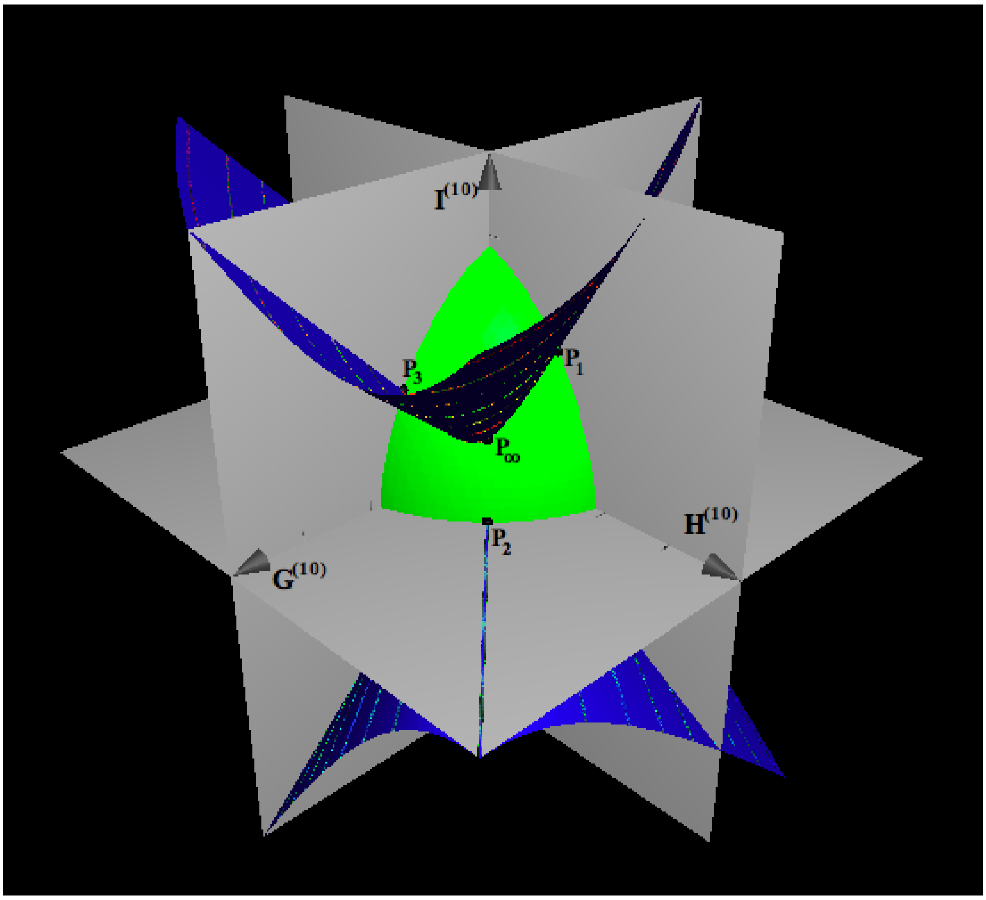

Figure 4: Cone (4.58) and ellipsoid (4.54) whose intersection contains the admissible solutions $d^{(10)}$.

Note that $\widetilde{Q}$ and obviously $\overline{Q}$ and Q_7 are positive Q values. As $Q \to +\infty$, there exists a unique solution point $P_\infty \in \mathcal{C}_{10}$, with coordinates

$$\begin{aligned} G_\infty^{(10)} &= \frac{h_n(a,b)}{h_d(a,b)} \left[-\frac{\rho_l}{2} + \sqrt{\left(\frac{\rho_l}{2}\right)^2 + \frac{h_d(a,b)}{h_n^2(a,b)}\, k_l} \right], \\ H_\infty^{(10)} &= a\, G_\infty^{(10)}, \\ I_\infty^{(10)} &= b\, G_\infty^{(10)}, \end{aligned} \tag{4.59}$$

where $h_n(a,b) = 2{+}2a{+}b$ and $h_d(a,b) = 2{+}2a^2{+}b^2{+}4\mathrm{e}^{-\gamma_l}a(b{+}1)$, with $a = \dfrac{1-2\mathrm{e}^{-\gamma_l}}{1-\mathrm{e}^{-\gamma_l}-\mathrm{e}^{-2\gamma_l}}$ and $b = \dfrac{1-2\mathrm{e}^{-\gamma_l}+\mathrm{e}^{-2\gamma_l}}{1-\mathrm{e}^{-\gamma_l}-\mathrm{e}^{-2\gamma_l}}$; similarly it is

$$\lim_{Q\to-\infty} P(Q) = P_\infty\,.$$

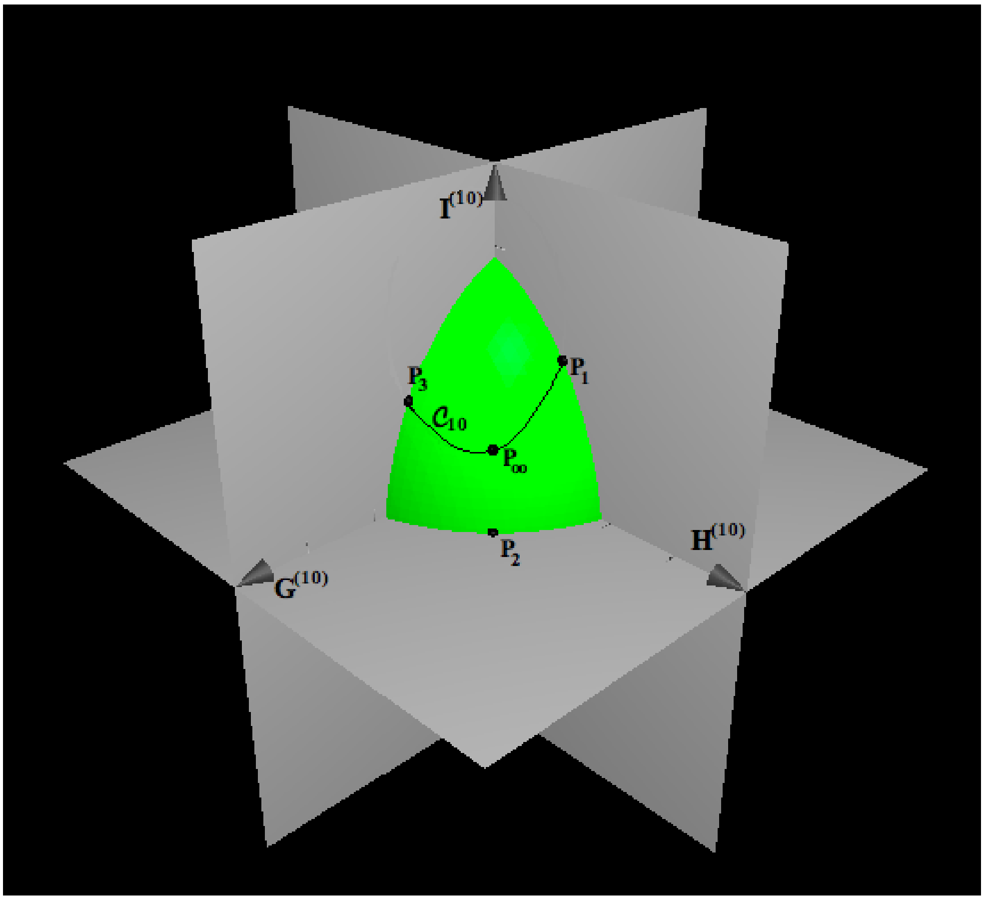

Figure 5: Arc of regular curve $\mathcal{C}_{10}$, intersection between the cone (4.58) and the ellipsoid (4.54), containing the admissible solutions $d^{(10)}$.

The limit point P_∞ can be found using the constraint (4.54) and observing that, for instance, from Equations (4.55) and (4.56), in the limit $|Q| \to \infty$ it must be

$$\left(1 - \mathrm{e}^{-\gamma_l}\right) G^{(10)} - \left(1 - \mathrm{e}^{-\gamma_l}\right) H^{(10)} - \mathrm{e}^{-\gamma_l} I^{(10)} = 0\,,$$

$$G^{(10)} - \mathrm{e}^{-\gamma_l} H^{(10)} - I^{(10)} = 0\,.$$

Therefore, starting from P_∞ there are two possible paths on $\mathcal{C}_{10}$ for the solution $P(Q)$: the first for Q increasing from $-\infty$ and the second for Q decreasing from $+\infty$. On each path, the solution $P(Q)$ moves continuously on $\mathcal{C}_{10}$ in a single direction from P_∞ to P_1, when $Q \uparrow \widetilde{Q}$, or from P_∞ to P_3, when $Q \downarrow \overline{Q}$. Considering for instance the first path, for any $Q' \in (-\infty, \widetilde{Q}]$, the point $P(Q')$ is the only real positive solution. In fact, if a different solution point $R(Q')$ existed on $\widehat{P_\infty P_1}$, then two different points would exist on $\widehat{P_\infty P_1}$ with the same value of Q'; consequently, a value $Q'' \in (-\infty, \widetilde{Q}]$, $Q'' \neq Q'$, would exist such that $P(Q'') \equiv R(Q')$, which is impossible in view of the linear dependence on Q of Equations (4.55)-(4.57). A similar argument applies to the second path $\widehat{P_\infty P_3}$ choosing $Q' \in [\overline{Q}, +\infty)$.

As we have to prove the inequality $J(d^{(10)}) > J(d^{(3)})$ for $0 < Q \leq \overline{Q}$, we do not care about $J(d^{(10)})$ for $Q \in (\overline{Q}, +\infty)$ but we just notice that for $Q = \overline{Q}$, it is $d^{(10)} \equiv d^{(3)}$, or $J(d^{(10)}) \equiv J(d^{(3)})$. For $Q = Q_7$ the solution is $d^{(10)} \equiv d^{(7)}$, and then $J(d^{(10)}) = J(d^{(7)}) > J(d^{(3)})$, as already stated (see Eqs. (4.29)-(4.31)). Finally, we are going to prove $J(d^{(10)}) > J(d^{(3)})$ for $Q \in (-\infty, \widetilde{Q}]$, and then $Q \in (0, \widetilde{Q}]$, which concludes the proof since the solution does not exist elsewhere. First, we note that no solutions can exist if $\lambda = 0$. In fact, from Eqs. (4.51)-(4.53) and (4.54) we get $G^{(10)} = H^{(10)} = I^{(10)} = Q = 0$ which is absurd and implies that λ must keep the same sign in a connected interval of Q, in which the solution exists. In particular, Eq. (4.51) for $Q = 0$ gives

$$\lambda = -\frac{H^{(10)}}{2G^{(10)} + \rho_l + 2\mathrm{e}^{-\gamma_l} H^{(10)}} < 0\,,$$

and then $\lambda < 0$ for all $Q \in (-\infty, \widetilde{Q}]$. Hence, Eq. (4.51) yields

$$H^{(10)} > Q\,. \tag{4.60}$$

Now we are able to prove the property

$$J(d^{(10)}) = -Q\left(2G^{(10)} + 2H^{(10)} + I^{(10)}\right) + 2H^{(10)}\left(G^{(10)} + I^{(10)}\right) > J(d^{(3)}) = -3QA_l^{(3)}\,.$$

Indeed, we have

$$\begin{aligned} J(d^{(10)}) &\geq -2Q\left(G^{(10)} + I^{(10)}\right) - 2QH^{(10)} + 2H^{(10)}\left(G^{(10)} + I^{(10)}\right) = \\ &= 2\left(G^{(10)} + I^{(10)}\right)\left(H^{(10)} - Q\right) - 2QH^{(10)} \geq -2QH^{(10)}\,, \end{aligned}$$

in view of (4.60). It is immediate to verify that the maximum value of $H^{(10)}$ is attained when $G^{(10)} = I^{(10)} = 0$ and it is equal to $A_l^{(2)}$. Finally, we can write

$$J(d^{(10)}) \geq -2QH^{(10)} \geq -2QA_l^{(2)} > -3QA_l^{(3)} = J(d^{(3)})\,,$$

in which the latter inequality follows from property (4.21). So the proof is complete. □

4.4 Optimal solution for $\mathbf{Q} > \overline{\mathbf{Q}}$.

The optimal solution provided by the theorem in the present section is valid for tumours having high α/β ratios (the pair of tumour parameters ρ, γ is such that $Q > \overline{Q}$).

Theorem 4.4 *For $Q > \overline{Q}$ the unique optimal solution is $d^{(10)}$, with dose values $G^{(10)}$, $H^{(10)}$, $I^{(10)}$ depending on Q, that is with optimal dose sizes depending not only on the late normal tissue but also on the tumour tissue.*

Proof As it has been seen in the proof of the previous section, the solution $d^{(10)}$ coincides with $d^{(3)}$ when $Q = \overline{Q}$, and it exists unique on the curve $\mathcal{C}_{10}$ when $Q > \overline{Q}$. The optimality of $d^{(10)}$ will be proved showing that no other solution exists for $Q > \overline{Q}$, since at least one multiplier η_j, $j = 1, \ldots, 5$, becomes negative. We recall that $d^{(10)}$ is the only class with $\eta_j = 0$, $j = 1, \ldots, 5$. Any other class $d^{(i)}$, $i \neq 10$, has at least one zero dose so that we can denote by I_z the set of indexes j related to zero doses. For the same indexes $j \in I_z$ it must be $\eta_j \geq 0$. Similarly, I_p denotes the set of indexes related to positive doses. Obviously, $\eta_j = 0$ for $j \in I_p$. In order to exclude the existence of classes $d^{(i)}$, $i \neq 10$, for $Q > \overline{Q}$, we basically applied the following procedure for $i = 1, \ldots, 9$:

- specialize the necessary conditions (4.2)-(4.4) to the structure $d^{(i)}$;
- express λ from one of the conditions having $\eta_j = 0$, $j \in I_p$;
- substitute the obtained λ in the remaining conditions so to express η_j, $j \in I_p$, as a function of Q and the positive doses;
- find the values of Q such that $\eta_j \geq 0$, $j \in I_z$;
- prove that the Q values found at the previous step are less than $\overline{Q}$, that is the solution $d^{(i)}$ cannot exist for $Q > \overline{Q}$.

We explicitly report the last two steps of the procedure for each class $d^{(i)}$, $i \neq 10$. More precisely, we actually report the condition $\eta_j \geq 0$, and the related condition on Q, for the particular $j \in I_z$ that assures the non existence of all the elements of the class.

I) Class $\boldsymbol{d^{(1)}}$.

Let us start by considering the class $d^{(1)}$. As already seen in Section 4.1, from Eqs. (4.12), (4.13) it follows that the solution $d^{(1)}$ exists if and only if $Q \leq 0$, and then $d^{(1)}$ even less exists for $Q > \overline{Q}$.

II) Class $\boldsymbol{d^{(2)}}$.

For the solution $d^{(2)}$ we have:

$$\eta_1 = \eta_5 = \frac{A_l^{(2)} \left[2A_l^{(2)} + \rho_l - 2Q\left(1 - \mathrm{e}^{-\gamma_l}\right) \right]}{\rho_l + 2A_l^{(2)}}\,, \tag{4.61}$$

with $A_l^{(2)}$ given in (4.14). Then, the multiplier (4.61) is non negative if and only if

$$Q \leq \frac{\rho_l + 2A_l^{(2)}}{2\left(1 - \mathrm{e}^{-\gamma_l}\right)} = Q_2\,,$$

Therefore, the existence of the whole class $d^{(2)}$ for $Q > \overline{Q}$ is excluded since $Q_2 < \overline{Q}$, as proved by the inequality (4.44).

III) Class $\boldsymbol{d^{(3)}}$.

Considering now the class $d^{(3)}$, as already seen in Section 4.3, from Eq. (4.20) it follows that the solution $d^{(3)}$ exists if and only if $Q \leq \overline{Q}$.

IV) Class $\boldsymbol{d^{(4)}}$.

For the solution $d^{(4)}$ we have:

$$\eta_5 = -\frac{B^{(4)}\left[\rho_l + 2Q\left(1 + \mathrm{e}^{-\gamma_l}\right)\right]}{\rho_l + 2B^{(4)}\left(1 + \mathrm{e}^{-\gamma_l}\right)},$$

obviously negative for $Q > \overline{Q}$, which guarantees the non existence of the class $d^{(4)}$ in this interval.

V) Class $\boldsymbol{d^{(5)}}$.

The class $d^{(5)}$ is the only class that requires to check the non-negativity of the multipliers for each element of the class, since there is not a single condition, in terms of Q, that excludes the existence of the whole class. There are, in fact, three possible kinds of multiplier depending on the position of the associated zero dose, which can be adjacent to: *i)* $A^{(5)}$ and 0, *ii)* $B^{(5)}$ and 0, *iii)* $A^{(5)}$ and $B^{(5)}$. They have the following expressions:

$$\eta^i = \frac{A^{(5)}\left(2A^{(5)} + \rho_l\right) - 2Q\left(1 - \mathrm{e}^{-\gamma_l}\right)}{2A^{(5)} + \rho_l},$$

$$\eta^{ii} = \frac{2B^{(5)}\left(B^{(5)} - Q\right)}{2\left(1 + \mathrm{e}^{-\gamma_l}\right)B^{(5)} + \rho_l},$$

$$\eta^{iii} = \frac{\left(A^{(5)} + B^{(5)}\right)\left(2A^{(5)} + \rho_l\right) - 2Q\left[\left(1 - \mathrm{e}^{-\gamma_l}\right)A^{(5)} - \mathrm{e}^{-\gamma_l}B^{(5)}\right]}{2A^{(5)} + \rho_l}.$$

Checking the non-negativity of η^i, η^{ii}, η^{iii}, respectively means checking the following conditions on Q:

$$Q \leq \frac{2A^{(5)} + \rho_l}{2\left(1 - \mathrm{e}^{-\gamma_l}\right)} \triangleq Q_5^i, \tag{4.62}$$

$$Q \leq B^{(5)} \triangleq Q_5^{ii}, \tag{4.63}$$

$$Q \leq \frac{\left(A^{(5)} + B^{(5)}\right)\left(2A^{(5)} + \rho_l\right)}{2\left[\left(1 - \mathrm{e}^{-\gamma_l}\right)A^{(5)} - \mathrm{e}^{-\gamma_l}B^{(5)}\right]} \triangleq Q_5^{iii}. \tag{4.64}$$

First we show that

$$Q_5^{ii} < Q_5^i < Q_5^{iii}. \tag{4.65}$$

Indeed, we have:

$$Q_5^{ii} = B^{(5)} < \left(1 + \mathrm{e}^{-\gamma_l}\right) B^{(5)} < A^{(5)} < \frac{2A^{(5)} + \rho_l}{2\left(1 - \mathrm{e}^{-\gamma_l}\right)} = Q_5^i \,,$$

where the inequality $\left(1 + \mathrm{e}^{-\gamma_l}\right) B^{(5)} < A^{(5)}$ holds because, taking the difference between two gradient conditions, we obtain:

$$B^{(5)} + 2\lambda \left[\left(1 + \mathrm{e}^{-\gamma_l}\right) B^{(5)} - A^{(5)}\right] = 0 \,. \tag{4.66}$$

Moreover, we know that

$$\lambda = \frac{Q}{2A^{(5)} + \rho_l} > 0 \,,$$

and, then, Eq. (4.66) requires $\left(1 + \mathrm{e}^{-\gamma_l}\right) B^{(5)} - A^{(5)} < 0$. On the other hand, it is

$$Q_5^i = \frac{2A^{(5)} + \rho_l}{2\left(1 - \mathrm{e}^{-\gamma_l}\right)} < \frac{\left(A^{(5)} + B^{(5)}\right)\left(2A^{(5)} + \rho_l\right)}{2\left[\left(1 - \mathrm{e}^{-\gamma_l}\right) A^{(5)} - \mathrm{e}^{-\gamma_l} B^{(5)}\right]} = Q_5^{iii} \,,$$

as it is

$$\frac{1}{\left(1 - \mathrm{e}^{-\gamma_l}\right)} < \frac{A^{(5)} + B^{(5)}}{\left(1 - \mathrm{e}^{-\gamma_l}\right) A^{(5)} - \mathrm{e}^{-\gamma_l} B^{(5)}} \,.$$

Now we want to stress that the existence of each element of the class $d^{(5)}$ is guaranteed by the non-negativity of a couple of multipliers, that is a pair of the three conditions on Q (4.62) - (4.64) must simultaneously hold. Each pair of conditions on Q is verified when Q is strictly lower than the smallest Q_5 in the pair. So, taking into account the property (4.65), each element of $d^{(5)}$ exists when $Q \leq Q_5^i$ or when $Q \leq Q_5^{ii}$. On the contrary, we can exclude the existence of the whole class $d^{(5)}$ when $Q > Q_5^i$ and, finally, when $Q > \overline{Q}$ if $Q_5^i < \overline{Q}$.

Let start the proof of the property $Q_5^i < \overline{Q}$ by noting that $A^{(5)} = 2B^{(5)}$ when $Q = Q_5^i$. This is easily obtainable from the necessary conditions setting $Q = Q_5^i$. By using the relation $A^{(5)} = 2B^{(5)}$ in the constraint (4.5) specialized to the structure $d^{(5)}$, we get the following equation for $A^{(5)}$:

$$\frac{3 + \mathrm{e}^{-\gamma_l}}{2} \left(A^{(5)}\right)^2 + 2\rho_l A^{(5)} - k_l = 0 \,,$$

which has the positive root $A^{(5)} = A_{Q_5^i}$. By rewriting Eq. (4.17) in terms of $2A^{(3)}$ as follows:

$$\frac{3}{4}\left(2A^{(3)}\right)^2 + \frac{3}{2}\rho_l \left(2A^{(3)}\right) - k_l = 0 \,,$$

we can easily understand that its positive root is such that $2A^{(3)} = 2A_l^{(3)} > A_{Q_5^i}$. This suffices to prove the following inequalities:

$$Q_5^i = \frac{2A_{Q_5^i} + \rho_l}{2\left(1 - \mathrm{e}^{-\gamma_l}\right)} < \frac{4A_l^{(3)} + \rho_l}{2\left(1 - \mathrm{e}^{-\gamma_l}\right)} < \frac{2A_l^{(3)} + \rho_l}{1 - 2\mathrm{e}^{-\gamma_l}} = \overline{Q} \,,$$

which guarantees the non-existence of $d^{(5)}$ for $Q > \overline{Q}$.

VI) Class $\boldsymbol{d^{(6)}}$.

For the solution $d^{(6)}$ we have:

$$\eta_1 = \eta_5 = \frac{C^{(6)}\left(2D^{(6)} - \rho_l\right) - 2Q\left(D^{(6)} + \mathrm{e}^{-\gamma_l} C^{(6)}\right)}{\rho_l + 2D^{(6)} + 4\mathrm{e}^{-\gamma_l} C^{(6)}} ,$$

which is negative if and only if

$$Q \leq \frac{C^{(6)}\left(2D^{(6)} - \rho_l\right)}{2\left(D^{(6)} + \mathrm{e}^{-\gamma_l} C^{(6)}\right)} \triangleq Q_6 .$$

We have

$$Q_6 < \frac{2C^{(6)}D^{(6)}}{2\left(D^{(6)} + \mathrm{e}^{-\gamma_l} C^{(6)}\right)} < C^{(6)} \leq A_l^{(2)} .$$

The latter inequality for $C^{(6)}$ can be easily derived from (4.5) imposing the structure $d^{(6)}$ and setting $D^{(6)} = 0$. It can be easily proved that $Q_6 < \overline{Q}$ by the following inequalities:

$$Q_6 < A_l^{(2)} < 2A_l^{(3)} < \overline{Q} .$$

VII) Class $\boldsymbol{d^{(7)}}$.

As already seen in Section 4.3, from Eq. (4.27) it follows that the solution $d^{(7)}$ exists if and only if $Q \leq Q_7$ (see Eq. (4.28)). Now we have to prove only that $Q_7 < \overline{Q}$. By rewriting the latter inequality as

$$4A_l^{(3)}\left(1 - \mathrm{e}^{-\gamma_l}\right) > 4B_l^{(7)}\left(1 - 2\mathrm{e}^{-\gamma_l}\right) - \rho_l ,$$

we can observe that it is certainly verified if $A_l^{(3)} > B_l^{(7)}$. This property is true since $A_l^{(3)}$ and $B_l^{(7)}$ are respectively the positive roots of Eqs. (4.17) and (4.24).

VIII) Class $\boldsymbol{d^{(8)}}$.

As to the class $d^{(8)}$, in Section 4.3 we have proved that the solution belongs to the curve $\mathcal{C}_8''$ for $Q > \overline{Q}$ (see Fig. 3). Nevertheless, this arc of the solution is not admissible because $\eta_4 < 0$ for $Q > \overline{Q}$, as we are going to prove in the following (in a slightly different way from the procedure given at the beginning of this proof). Let us start by specializing the necessary conditions to the class $d^{(8)}$ and in particular the condition providing the expression of η_4:

$$\eta_4 = -Q + A^{(8)} + C^{(8)} + \lambda\left[\rho_l + 2\mathrm{e}^{-\gamma_l}\left(A^{(8)} + C^{(8)}\right)\right] . \tag{4.67}$$

By subtracting from (4.67) one of the remaining gradient conditions and by substituting the expression of λ given by the first of Eqs. (4.34), we obtain

$$\eta_4 = \frac{\left(A^{(8)} - C^{(8)} - D^{(8)}\right)\left(A^{(8)} - C^{(8)} + D^{(8)}\right)}{\left(A^{(8)} - C^{(8)} - \mathrm{e}^{-\gamma_l} D^{(8)}\right)} .$$

Let us search for possible zeroes of η_4 when $Q > \overline{Q}$. This consists in searching for the zeroes of the factor $\left(A^{(8)} - C^{(8)} - D^{(8)}\right)$ in that the denominator of η_4 is strictly positive, as shown in Eq. (4.35), and the factor $\left(A^{(8)} - C^{(8)} + D^{(8)}\right)$ is also positive in region $\mathcal{B}$ (see Fig. 1). So, for $Q > \overline{Q}$, $\eta_4 = 0$ if and only if

$$A^{(8)} - C^{(8)} = D^{(8)} .$$

Using the previous relation in (4.42), we obtain $C^{(8)} = 0$ and then, from (4.32), the solution $\left(A_l^{(2)}, 0, A_l^{(2)}\right)^T$ corresponding to $Q = Q_2$. Hence, η_4 cannot vanish for $Q > \overline{Q}$, since $Q_2 < \overline{Q}$. Finally, it is immediate to verify from Eq. (4.67) that $\eta_4 < 0$ for all $Q \in (\overline{Q}, +\infty)$, since $\eta_4 \to -\infty$ when $Q \to +\infty$, which guarantees the non-existence of $d^{(8)}$ in the interval of interest.

IX) Class $\boldsymbol{d^{(9)}}$.

The class $d^{(9)}$ is similar to $d^{(6)}$. In fact, we have:

$$\eta_5 = \frac{F^{(9)}\left[2E^{(9)} - \rho_l - 2Q\left(1 + \mathrm{e}^{-\gamma_l}\right)\right]}{\rho_l + 2\mathrm{e}^{-\gamma_l} E^{(9)} + 2\left(1 + \mathrm{e}^{-\gamma_l}\right) F^{(9)}} ,$$

which is negative if and only if

$$Q \leq \frac{2E^{(9)} - \rho_l}{2\left(1 + \mathrm{e}^{-\gamma_l}\right)} = Q_9 .$$

We have

$$Q_9 < \frac{E^{(9)}}{1 + \mathrm{e}^{-\gamma_l}} < E^{(9)} \leq A_l^{(2)} .$$

The latter inequality for $E^{(9)}$ can be easily derived from (4.5) imposing the structure $d^{(9)}$ and setting $F^{(9)} = 0$. As done for class $d^{(6)}$, the property $Q_9 < \overline{Q}$ readily follows from

$$Q_9 < A_l^{(2)} < 2A_l^{(3)} < \overline{Q} .$$

□

5 Some concluding remarks about the optimal solutions.

Let us remark some aspects about the optimal solutions provided by the theorems of Section 4. First, we note that the structure of the optimal solutions depends on both tumour and normal tissue, that is, in our formulation, on the global parameter Q. At least for $Q \leq \overline{Q}$, the size of the optimal doses depends instead only on the normal tissue parameters.

The condition $Q = 0$ ($\rho = \rho_l$), giving three optimal solutions for Problem 2.1, must be considered as a limit case because tumour and normal tissues are indistinguishable. Actually, for $i = 1, 2, 3$, the cost functions $J(d^{(i)})$ do not contain the interaction term $\tilde{E}_2$ given in Eq. (2.4) and then it is $J(d^{(i)}) \equiv 0$.

A further remark is that for no value of Q, the five doses of the optimal solution are equal: this is obvious for the optimal solutions of Subsections 4.1, 4.2, 4.3, in which some of the optimal doses are zero. On the contrary, all the doses of the optimal solution of Section 4.4 are positive but never equal, as $G^{(10)}(Q) > I^{(10)}(Q) > H^{(10)}(Q)$, even for $Q \to +\infty$. The optimal solution becomes uniform only in the limit $\gamma, \gamma_l \to +\infty$ (and for $\rho > \rho_l$), that is in the absence of interactions between adjacent doses (see [1]). Figure 6 qualitatively shows different patterns of the optimal solution in four intervals of Q, $Q \neq 0$.

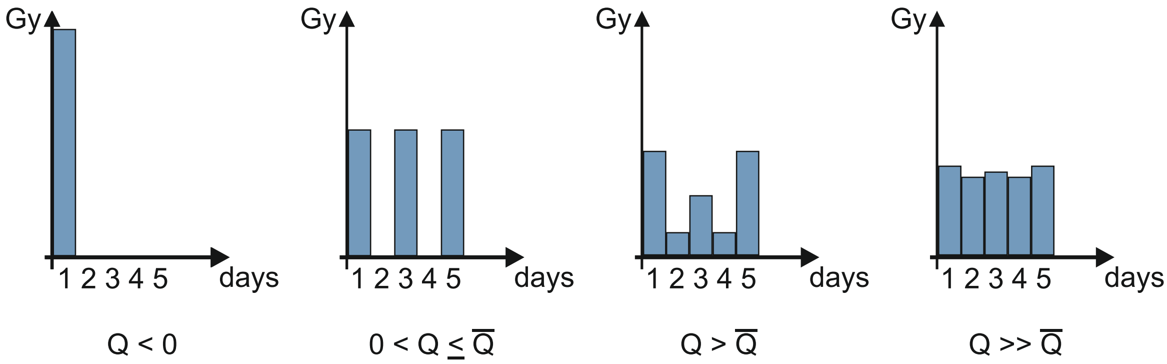

Figure 6: Patterns of the optimal solution for different Q values.

In order to numerically compute the optimal solution of Problem 2.1, and in general of the problem with both early and late constraints, the maximal damage to normal tissues must be assigned. It is common in the literature [19, 3] to assume the maximal admissible damage to normal tissues equal to the damage produced by a given reference protocol consisting of five equal doses $\bar{d}$ per week. The damage is usually assumed proportional to the logarithm of the inverse cell survival. Therefore, given a radiotherapy protocol, the damage level it produces on a tissue depends on the model chosen to represent the tissue response to radiation. A quantity very often used in radiology to express the damage is the Biologically Effective Dose (BED) that represents the ratio between total damage and radiosensitivity parameter α. With regard to late responding tissues we have

$$\mathrm{BED}_l = 5\nu\bar{d}\left(1+\frac{\bar{d}}{\rho_l}\right) ,$$

where 5ν is the total number of doses. Correspondingly, recalling notation (2.7) with $f=1$, we have

$$k_l = \rho_l \frac{\mathrm{BED}_l}{\nu} = \rho_l 5\bar{d}\left(1+\frac{\bar{d}}{\rho_l}\right) . \tag{5.1}$$

For the early responding normal tissue, taking into account the cell repopulation term, we have

$$k_e = \rho_e 5\bar{d}\left(1+\frac{\bar{d}}{\rho_e}\right) . \tag{5.2}$$

If the maximal damages per week, k_l and k_e, are computed as (5.1) and (5.2), which is commonly done in the literature by fixing the maximal BED of normal tissues [19, 3], the late constraint (2.9) prevails on the early constraint (2.8). Then, the general optimization problem having both constraints is equivalent to the simpler one described in the present work, as shown in [1].

The damages produced by the reference protocol to normal tissues can be computed also according to the LQ model including the incomplete repair term, that is

$$k_l = \rho_l 5\bar{d}\left(1+\frac{\bar{d}}{\rho_l}\right) + 8\mathrm{e}^{-\gamma_l}\bar{d}^2 ,$$

$$k_e = \rho_e 5\bar{d}\left(1+\frac{\bar{d}}{\rho_e}\right) + 8\mathrm{e}^{-\gamma_e}\bar{d}^2 .$$

However, in this case the early constraint is not negligible and the optimization problem here studied is not equivalent to the general one, see Sections 2 and 3 in [1].

According to the problem studied in this work, we computed k_l as in (5.1) and we evaluated the qualitative behaviour of single and total optimal doses for $Q \in (\overline{Q}, +\infty)$, that is the interval where the optimal doses actually change with Q. The function $\mathcal{D}^{(10)}(Q)$ is monotonically increasing from the value

$$\mathcal{D}^{(10)}(\overline{Q}) = 3A_l^{(3)} = 3\left[-\frac{\rho_l}{2}+\sqrt{\left(\frac{\rho_l}{2}\right)^2+\frac{k_l}{3}}\,\right] ,$$

to the value

$$\begin{aligned}\mathcal{D}_\infty^{(10)} &= \lim_{Q\to+\infty}\mathcal{D}^{(10)}(Q) = \\ &= \frac{h_n^2(a,b)}{h_d(a,b)}\left[-\frac{\rho_l}{2}+\sqrt{\left(\frac{\rho_l}{2}\right)^2+\frac{h_d(a,b)}{h_n^2(a,b)}\,k_l}\,\right] < 5\bar{d} .\end{aligned}$$

For γ_l sufficiently large, the ratio $\dfrac{h_n^2(a,b)}{h_d(a,b)}$ tends to 5 and $\mathcal{D}_\infty^{(10)} \to 5\bar{d}$.

As far as the single optimal doses are concerned, it can be verified that the first and the fifth component of $d^{(10)}$, $G^{(10)}(Q)$, monotonically decrease from $A_l^{(3)}$ to $G_\infty^{(10)}$ in (4.59); the second and fourth doses, $H^{(10)}(Q)$ monotonically increase from zero to $H_\infty^{(10)}$ in (4.59); the central dose $I^{(10)}(Q)$ decreases at first from $A_l^{(3)}$ to its minimum value

$$I_{\min}^{(10)} = \frac{20}{21+27\mathrm{e}^{-\gamma_l}}\left[-\frac{\rho_l}{2}+\sqrt{\left(\frac{\rho_l}{2}\right)^2+k_l\frac{21+27\mathrm{e}^{-\gamma_l}}{100}}\,\right],$$

and then it increases up to the final value $I_\infty^{(10)}$ in (4.59). Figure 7 reports the simulated behaviours using the notations of Table 1.

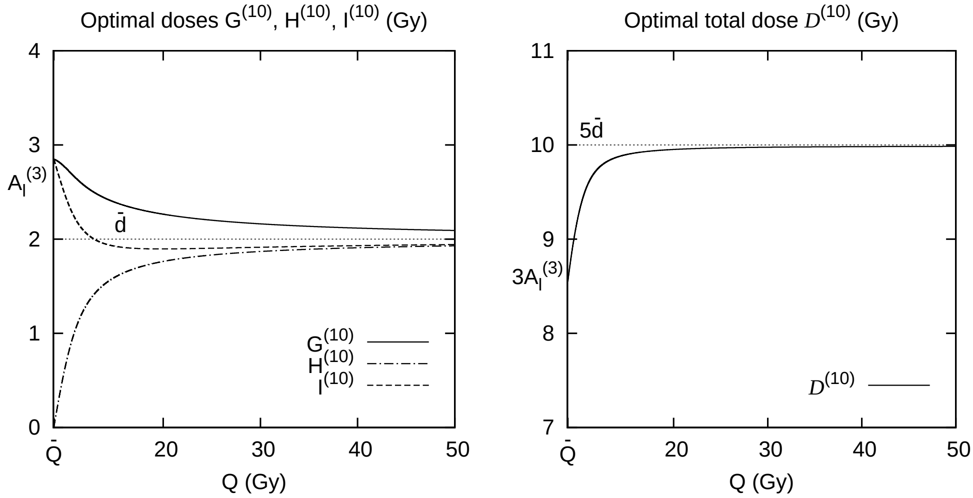

Figure 7: Behaviour of the single and total optimal doses for $Q \in (\overline{Q}, 50]$ with $\overline{Q} = 8.7$, assuming $\rho_l = 3$ Gy, $\gamma_l = 6$, $\bar{d} = 2$ Gy.

As a last point we remark that, given the late normal tissue parameters and the global parameter Q, the optimal solution does not represent the optimal treatment for a single tumour type, but rather for a class of tumours. Indeed, given a value of Q there exist an infinity of pairs (ρ, γ) satisfying the definition (3.1) of Q.

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